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13. ABSTRACT *(Maximum 200 words)*

During the last 11 months of this project, the Cancer and Leukemia Group B (CALGB) entered 103 breast cancer patients into the Linked Registry according to procedures specified in CALGB protocol 9484. The telephone interviews have gone smoothly, and the data entry is proceeding without difficulty. The flow of samples from these patients has been most satisfactory and there have been no problems with preparation of DNA from them, or with the handling of serum samples and tissue blocks. During year four accrual has increased substantially as a result of actions taken during year three. However, it is still less than originally anticipated for this project. Because of this, a no-cost one year extension of the project was requested and was subsequently approved by the sponsor. The Steering Committee has met and reviewed alternate projects for which a smaller than anticipated Registry will be of value. Although it was expected that samples would be provided to investigators during year four of the project, it has been decided to await the collection and integration of the additional samples and information that will be derived during year five of this project before committing samples for study.

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FOREWORD

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O Ross Mitchell October 6, 1998

PI - Signature Date

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Progress Report
Contract DAMD 17-94-J- 4114 from U.S. Army Research and Materiel Command

October 1, 1997-September 30, 1998

Prepared by O. Ross McIntrye, M.D. Principal Investigator

I. INTRODUCTION:

A. Nature of the problem:

The use of adjuvant chemotherapy following local treatment of the tumor has clearly benefited many patients with breast cancer[1]. On the other hand, adjuvant chemotherapy carries with it a number of potential risks including secondary malignancies. Thus, it would be desirable to give adjuvant therapy only to the subgroup of women with breast cancer who are most likely to have a recurrence. Although clinical findings are useful in assigning prognosis [2,3], these alone are imperfect measures and there is hope that additional tests, such as the detection of certain somatic mutations in the tumor, will prove helpful in guiding the decision as to who should and who should not receive adjuvant chemotherapy. These considerations have now been formalized in the language describing such testing and a distinction between prognostic factors (which forecast clinical outcome) and predictive factors (which predict response and influence selection of specific forms of therapy) has been offered.[4]

In addition to our ability to detect a number of somatic mutations that may predict the risk of recurrence, it is now possible to identify those individuals who carry mutations in the BRCA 1 or BRCA 2 gene in their germline[5,6,7,8,9,10]. It is anticipated that additional genes conferring an increased risk of breast cancer upon their carriers will be identified. The presence or absence of susceptibility alleles in the germline may influence not only risk of occurrence of breast cancer but also the response to treatment and other outcomes in these patients. Knowledge that such genes are present may predict the likelihood of a second primary in women who have already been diagnosed with breast cancer, and may assist in guiding prevention efforts in other members of the family who carry the gene.

Because interactions of erbB-2 and p53 with type of adjuvant therapy received have already been observed (see next section), it is important that assays for putative prognostic factors be performed on well-characterized groups of patients receiving adjuvant chemotherapy according to standardized protocols. The registry being created with support from this grant is quite different from usual population-based registry concepts. Instead, it may be viewed as a library in

which clinical information on groups of uniformly staged and treated patients is located within a structure that also contains each patient's personal, family, and environmental exposure history, specimens from patients, and data from molecular and other laboratory studies. In contrast to a population-based registry, it offers an internally cohesive group of patients with well-defined disease, treatment and follow-up. It is possible to draw scientifically valid conclusions from this group by looking for interactions between treatment and factors such as genomic susceptibility and acquired somatic alterations.[11]

In cohorts of patients treated on our protocols, endpoints such as time to recurrence, site of first recurrence, percentage of planned adjuvant therapy received, and detailed initial staging information are systematically recorded. Moreover, there is an opportunity to collect additional information (dietary, smoking, and exposure history) from such patients that may be useful in predicting the likelihood of a germline mutation or other factors that may interact with treatment and prognosis.

The identification in a patient or family member of a breast cancer patient of a heritable gene conferring an increased risk of breast cancer carries with it economic and psychosocial risks[12] in addition to the possibility that the gene is not causally related to the cancer in that patient[13]. We will be able to assess the impact of determining genomic susceptibility on individuals *most in need* of this type of information. The creation of the linked registry supported by this grant offers the opportunity for the patients and those involved in the laboratory to be joined in the pursuit of new knowledge. It is important that this pursuit be conducted in a manner offering the least psychological stress and the greatest protection from adverse social and economic consequences to those who participate. Collection of detailed information at the time of entry to the study relating to this as well as other areas will allow hypotheses concerning this aspect of the study to be tested.

B. Background and Previous Work

In order to show the value of our linked-registry we offer the example that follows. We emphasize that this is an early example of the type of success we hope to achieve. The work that produced these results followed the successful integration of effort by a number of individuals, funded by a variety of sources including NCI grants to the CALGB, R01 and SPORE grants held by certain of the investigators, and by a small foundation grant to the CALGB.

Example: In 1989, the CALGB activated protocol 8869 with Hyman Muss, M.D. as study chair. The goal of this study was to pursue possible relationships between S phase and ploidy in breast cancer specimens, as determined by flow cytometry techniques, with clinical outcome in patients treated on our adjuvant protocol 8541. The protocol provided for collection of fixed tissue on a random sample of patients entered on the treatment study. As 8869 progressed, and as techniques

were perfected for the immunohistochemical determination of erbB-2 and P53 on paraffin embedded specimens, the protocol was amended so that Ann Thor, M.D., then of Massachusetts General Hospital, could apply these tests to the specimens. In addition, molecular assessment of these tissues by Edison Liu, M.D., of the University of North Carolina was added at that time.

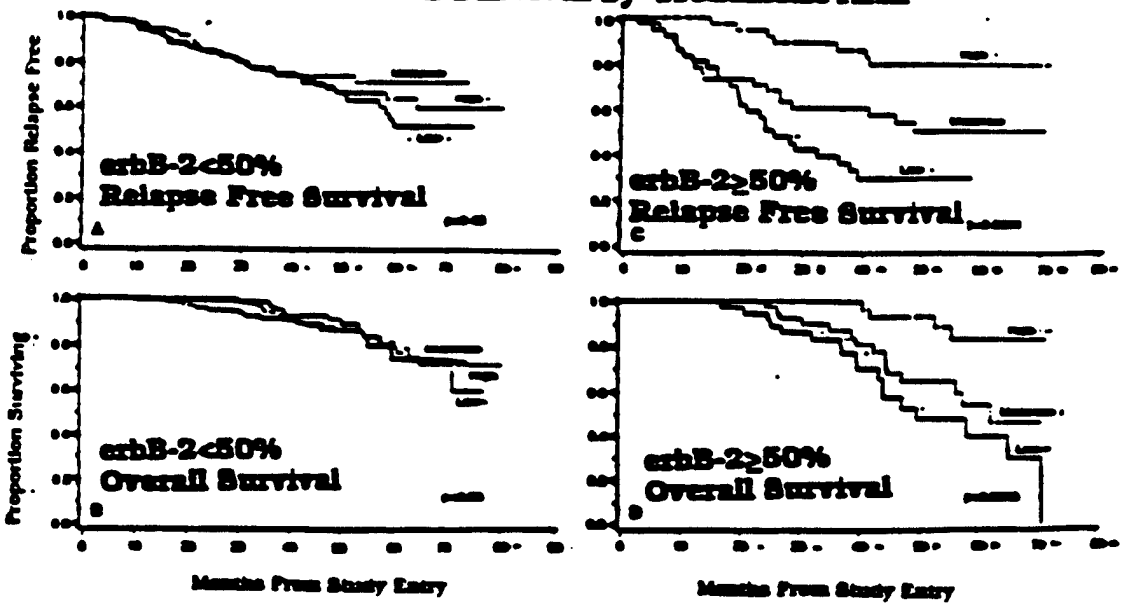
The treatment protocol, 8541, tested three CAF (cyclophosphamide, doxorubicin, and 5-fluorouracil) adjuvant regimens for which the dose schedule and dose intensity are shown in Table 1. Patients receiving the more dose intense regimens had significantly longer disease-free and overall survival than patients receiving the lower dose regimen.[14,15]

Table 1
Dose and Dose-Rates

Arm	I	II	III
Dose Rate mg/M2/week			
Cyclophosphamide	150	100	75
Doxorubicin	15	10	7.5
5-Fluorouracil	300	200	150
Cumulative Dose mg/M2			
Cyclophosphamide	2400	2400	1200
Doxorubicin	240	240	120
5-Fluorouracil	4800	4800	2400

When these treatment results are combined with studies of S-phase, P53 and erbB-2, an unexpected highly significant finding emerged.[16,17] The effect was most dramatic for erbB-2 which is shown in Figure 1, although similar results occurred when P53 overexpression[18,19] or S-phase were analyzed.

Figure 1
erbB-2 and Survival by Treatment Arm



As shown, the patients whose tumors overexpressed erbB-2 had a significantly longer disease-free and overall survival than those whose tumors did not overexpress erbB-2. There was no significant difference in disease-free or overall survival with any of the three treatments for those patients whose tumors did not overexpress erbB-2. These findings indicate that the benefit of intensive adjuvant therapy with this combination is limited to a subgroup of patients. From the clinical data we know that the group receiving the more intensive treatments fared better, but without the integrated laboratory data, of course, we would have no indication that this intensive treatment group was comprised of two populations, one which did, and the other which did not, benefit from the more intensive treatments.

As stated above, 8869 originally collected specimens on a randomly selected sample of all patients on 8541. Committing almost all of the very limited non-NCI funds available to the CALGB, we immediately set about to collect and study all of the remaining blocks available from patients on this study. The outcome of this testing has just been reported [20] and supports the hypothesis that the benefits of doxorubicin treatment in node positive breast cancer patients are restricted to those patients overexpressing erbB-2. Another cooperative group, acting on the information provided by our earlier report, has examined the possible interaction of erbB-2 overexpression and doxorubicin treatment in node negative breast cancer patients and has reached similar conclusions in this population.[21] Although it remains necessary to develop reliable and standardized methods for assessment of erbB-2 and other predictors of doxorubicin response before these results will have widespread clinical application, it appears that we are on the threshold of a major change in the way that patients will be assigned to adjuvant regimens[22].

Conclusion from the Example: The issue of dose intensity, time to failure or death, and erbB-2 (or P53) overexpression would not have been raised if the laboratory study had not been conducted on tissue samples of similarly staged patients receiving randomly assigned, defined therapeutic regimens.

The rapidly building capabilities for this type of study and the excitement attending the initial success of combining laboratory and clinical information on our patients has led to several meetings of investigators. At these meetings there has been vigorous discussion of the opportunities for new projects as well as the need to develop new resources to serve CALGB as well as other investigators. The infrastructure category of the Army BAA offered an ideal mechanism to advance our studies and to assist other investigators in the field.

C. Purpose and Hypothesis:

We are using well-established methods within the CALGB and new procedures developed with support of this project to create a specialized registry which links molecular and epidemiological data with data from uniformly staged breast

cancer patients receiving defined therapy. This registry of data, tumor tissue, and other specimens will enhance the research of peer reviewed and funded investigators during the course of the project. It is intended that the level of quality control as well as the comprehensiveness of the registry will make it an unparalleled resource for investigators pursuing the relationship between tumor genetics, tumor biology and the prevention and treatment of breast cancer.

D. Methods of Approach - Specific Technical Objectives:

This project creates a linked-registry based upon the capabilities of CALGB to rapidly enroll large numbers of well-characterized incident breast cancer patients to its treatment trials. It takes advantage of a unique opportunity to link data on the biology of breast cancer with information on uniformly staged patients who receive defined treatments. Since TNM staging defines rather broad categories[23], especially in stage II breast cancer, we anticipate that an exploration of the sources of heterogeneity with newly developed markers will advance our understanding of the disease.

This registry is used for studies on epidemiological and molecular characteristics that influence the outcome for breast cancer patients. The registry will provide information critical to the design of future chemo-prevention studies, the interaction of treatment with factors that govern disease progression and metastasis, and will be instrumental in guiding the design of future adjuvant treatment trials.

Specific technical objectives are as follows:

a. To modify questionnaires currently in use by CALGB investigators at the University of North Carolina, University of Minnesota and NIEHS to collect key family history and exposure data in a self-completed questionnaire.

b. To establish review procedures and criteria for selecting patients with a family cancer history for further study. Criteria will include, but are not limited to, having one or more first-degree relatives with breast cancer or having 2 or more relatives with breast, ovarian, or colon cancer.

c. To develop a telephone interview with patients identified for further study that will expand on the screening data collected, obtain information that will facilitate validation of cancer reported, and locate selected siblings for inclusion in the database.

d. To collect fixed breast tissue from patients and germ-line DNA, plasma, and urine from the same patients.

e. To review and confirm the histopathological diagnosis of breast cancer on submitted tissue.

f. To integrate information about specimen receipt, specimen availability, and laboratory testing results with the CALGB database and to prioritize use of this information.

g. To modify the CALGB database and data handling procedures at the CALGB Statistical and Data Management Center at Duke University, so as to efficiently capture and record information from the registry, and to furnish it to users.

h. To augment resources at CALGB institutions in order to procure the above described information and specimens.

II. BODY OF THE APPLICATION

A. Description of the Methods:

In contrast to laboratory-based investigations, the linked registry employs new and existing committees of the CALGB and new resources created by the registry to collect specimens as well as epidemiologic and psychosocial information. It provides a mechanism to integrate registry data with clinical information derived from CALGB clinical trials. Specimens and information from the registry are to be used by laboratory-based investigators, epidemiologists, and others to test various hypotheses bearing on breast cancer cause, risk, progression, response to treatment, as well as to determine the psychosocial impact of this testing.

This project is based at Dartmouth Medical School where Dr. McIntyre, the Principal Investigator, serves as the James Carroll Professor of Oncology, Emeritus. Subcontracts from Dartmouth provide support for activities at the University of North Carolina (DNA extraction and epidemiology), Georgetown University (Lombardi Cancer Center - serum and urine bank), Roswell Park Cancer Institute (tissue sectioning, tissue banking and pathology review), the University of Chicago (communication, protocol editing, and regulatory compliance) and Duke University (statistics and data management). Where possible, efficiencies are achieved by using methods of communication, data submission, protocol editing, meeting arrangements, etc., that have been developed for the CALGB.

The Principal Investigator, Dr. McIntyre, is assisted in the management of the project by three committees:

Table 2
Linked Registry Steering Committee

Name	CALGB position	Institution
O. Ross McIntyre, M.D.	Committee Chair	Dartmouth
Robert Millikan, DVM, Ph.D	Co-PI	U. North Carolina
Carolyn Compton, M.D.	Pathology Com. Chm	Mass. General
Donald Berry, Ph.D.	Statistician	Duke Univ.
Ira Bleiweiss, M.D	Pathologist	Mount Sinai
Daniel Hayes, M.D.	Cor. Sci. Chm.	Georgetown Univ.
Larry Norton, M.D.	Br. Com. Chm	MSKCC
Lauren Schnaper, M.D.	Surgery	External Member
Lynn Dressler, M.A.	Cor. Sci. Com.	U. North Carolina
Dale Sandler, Ph.D.	Epidemiologist	NIEHS
Debra Collyar	Patient Advocate	External Member
Susan Moore	Patient Advocate	External Member

This interdisciplinary committee is responsible for overseeing the conduct of the project, assisting with the integration of projects that will use the registry so as to

insure the greatest productivity from it, and setting priorities for use of the resource.

Epidemiology Resource Committee: This committee is responsible for the design of the data collection instruments employed by the linked registry. It is also responsible for the review and prioritization of projects requesting use of linked registry data. The committee is chaired by Dale Sandler, Ph.D, Chief, Environmental and Molecular Epidemiology Branch, NIEHS.

Table 3
Epidemiology Resource Committee

Name	CALGB position	Institution
Dale Sandler, Ph.D.	Chair	NIEHS
Robert Millikan, DVM, Ph.D.	Co P.I.	U. North Carolina
Beth Newman	Epidemiologist	U. North Carolina
Stephanie London MD, Ph.D.	Epidemiologist	Univ. So. Cal.
Matthew Longnecker, MD, ScD	Epidemiologist	UCLA
Thomas Sellers, Ph.D.	Epidemiologist	U. Minnesota
Fred Li, M.D.	Epidemiologist	Dana Farber
Donald Berry, Ph.D.	Statistician	Duke University
Virginia Ernster Ph.D.	Epidemiologist	U. of California S.F.
Lauren Schnaper, M.D.	Surgeon	Greater Baltimore M.C.

In brief, the committee has developed and implemented procedures to collect family cancer history, reproductive and hormone use history, and other exposure information from all breast cancer patients enrolled in CALGB treatment trials. Tumor tissue and germ-line DNA is collected from breast cancer patients as described below.

Breast cancer patients who are registered to CALGB treatment trials are informed by CALGB clinical research associates and nurse oncologists about this project at those CALGB institutions where CALGB 9484 has been activated. Patients are offered the opportunity to participate in a treatment companion protocol, CALGB 9484, that provides for the gathering of epidemiological data and collection of specimens. In 1996 the protocol was amended with the expectation that the changes would improve patient accrual. When accrual remained lower than desirable, additional changes to the protocol and the consent form were approved by the CALGB and the Army in 1998. The rationale for the changes embodied in the most recent version of the protocol are given in section B, below. The methods described in this section are those specified in the amended protocol and differ somewhat from procedures described in previous progress reports.

Breast cancer patients who give their informed consent for treatment on selected CALGB breast cancer protocols are asked to return a self-completed questionnaire and to give permission for submission of their biopsy specimen as well as blood

and urine samples. In addition we ask the patient's permission to conduct studies of germline DNA on cells obtained from a blood sample. The consent form for these procedures is based upon the simplified consent form developed under the leadership of the National Action Plan on Breast Cancer and the National Cancer Institute. Following the development of this simplified consent, the Army approved a consent form based upon these principles for this project. The self-completed questionnaire was appended to the progress report for year 2 of the project.

Questionnaires are collected by the institutional clinical research associates who submit them to the CALGB Data Management Center at Duke. There, they are examined for completeness, checked for errors, and the data entered in the CALGB database.

On the basis of information from the self-completed questionnaire, the investigators at UNC, under the direction of Dr. Millikan, categorize the patients into three groups:

a. Patients with any first or second degree relative with breast or ovarian cancer.
b. Patients aged <50 years with no family history.
c. Patients aged ≥ 50 years with no family history.

All patients in the above groups a and b, and, a random sample of group c, are contacted by the telephone interviewer. Consenting patients are then queried in the telephone interview. The questionnaire administered by telephone was furnished in Appendix 2 of the progress report for year 2 of the project.

Our previous experience has shown that it is necessary to conduct telephone or in-person interviews to verify and complete family histories and exposure history. Because recall bias is introduced in self-reports of breast cancer occurrence in first degree relatives[24] a carefully administered interview to confirm the self-reporting is indicated. Telephone interviews work as well as in-person interviews for this purpose.[25,26]

We have found an 85% participation rate in our telephone interview inquiring about risk factors for leukemia and this is carried out while these acutely ill patients are hospitalized. While the response rate for the self-completed questionnaires is often lower than that for telephone or in-person interviews, we anticipate a high rate of return of the initial questionnaire because institutional data managers are responsible for retrieving the completed forms. We have used telephone interviews with great success not only in the environmental exposure studies in leukemia patients but also in the long-term follow-up of patients with successfully treated Hodgkin's disease.[27,28,29]

Tissue Resource Coordinating Committee: The Breast Tissue Coordinating Committee, Chaired by Lynn Dressler, University of North Carolina, serves to coordinate the systematic collection and archiving of breast tissue, germ-line DNA, serum, plasma, and urine.

Table 4

Tissue Resource Coordinating Committee

Name	CALGB position	Institution
Lynn Dressler M.A.	Chair	U. of North Carolina
Robert Millikan, MPH, Ph.D.	Co P.I.	U. of North Carolina
Carolyn Compton, M.D., Ph.D.	Pathology	Mass. General
Joe Gray, Ph.D.	Genetics	U. of California S.F.
Daniel Hayes, M.D.	Oncology	Georgetown
Hyman Muss, M.D.	Oncology	University of Vermont
Donald Berry, Ph.D	Statistician	Duke University

1. Fixed tissue:

When the patient signs an informed consent to participate in CALGB 9484 institutional data managers arrange for submission of tissue blocks by contacting the coordinating pathologist at a CALGB main member or affiliate institution. Paraffin blocks and sample submission forms are received at the CALGB Pathology Office directed by Dr. Maurice Barcos at Roswell Park Cancer Institute. During the next year of the project, the Pathology Office will move from Roswell Park Cancer Institute to the laboratory of Dr. Carolyn Compton at the Massachusetts General Hospital. Approval for transfer of the subcontract supporting the pathology activities relating to this project has been given by the Army. Four micron slides are reviewed for accuracy of diagnosis, and areas on the slides containing homogeneous malignant tissue are delineated. The blocks are trimmed, if necessary, to yield 4 (immunohistochemistry) and 10 micron sections (PCR, FISH) of homogeneous tumor, as well as non-malignant breast tissue. At least 30 sections are removed: 20, 4 micron sections for immunohistochemistry/FISH/IHC assays and 10, 10 micron sections for molecular based assays requiring extracted DNA. At three levels, sections are taken and stained and examined to ensure representative tissues is being distributed for all assays. We ask for permission to retain the blocks for future sectioning and store them at 4° C. If this is not granted, we prepare sections as described above, as determined by the amount of tissue available in the block. Prior to the return of the blocks to the submitting institution we prepare additional sections.

2. DNA procurement:

Somatic DNA: From the specimens collected as described above, individual investigators prepare somatic DNA according to their established laboratory procedures.

Germline DNA: EDTA anticoagulated peripheral blood is collected and shipped to the UNC DNA extraction laboratory overnight for lymphocyte separation and DNA extraction. Lymphocyte DNA is prepared using the ABI DNA extractor and the DNA stored at -70°C. Yield and quality of extracted DNA are monitored on an ongoing basis.

Quality control/quality assurance/sample distribution for DNA extraction:

The CALGB Pathology Office cuts and mounts a series of 10 micron sections on uncoated slides from each block according to their routine procedures. These procedures incorporate careful quality control and quality assurance parameters, including changing the microtome blade between each block to prevent contamination of DNA on the blade surface, cleaning the waterbath surface between each block, and wearing gloves to process blocks. As part of the routine processing procedure at the RPCI Pathology Office, sections for H & E staining are cut immediately preceding and after those cut for molecular (10 micron section) and immunohistochemical (4 micron) assays. The CALGB Pathology Office reviews all H & E sections to ensure that representative and sufficient tumor tissue is present throughout all sections cut for assay. In addition, to enrich for tumor tissue, tumor-rich versus tumor-poor areas are marked on the corresponding H & E section(s). For DNA processing, the corresponding H & E section will be superimposed on the unstained 10 micron sections and the circled region of tumor rich areas will be isolated and scraped into an Eppendorf tube by the technician in the UNC tissue bank. DNA lysates will be prepared as described below from each tumor tissue. DNA lysates are stored at 4 degrees centigrade for short term storage and at -85 degrees centigrade for long term banking. DNA lysates are stored in vials and multiple aliquots of processed DNA are prepared. As indicated above, DNA processing occurs in a clean area: a special room where only tissue and DNA processing is allowed to prevent DNA contamination, a major problem in PCR based studies. Distribution of samples is defined in the CALGB protocol and is rigorously monitored both in house and through the CALGB Labtrak system. A protocol is only developed once the study has received appropriate review and approval from the Solid Tumor Correlative Science Committee and Central Tissue Bank Committee.

Protocol for DNA Extraction from Tissue Sections:

Formalin fixed paraffin embedded tissue sections (1-5 depending on cellularity and size of tumor area) are gently scraped from uncoated glass slides (uncoated slides facilitates the scraping process, although tissue can be scraped from coated slides as well) with a 200 ul micropipet tip into a 1.5 microfuge tube. In a fume hood, 500 ul of xylene is added to each tube and the tubes are thoroughly mixed. After a 5 minute centrifugation at 1200 rpm, the supernatant is discarded into a xylene waste container, and the pellet is extracted twice with 500 ul of autoclaved 95% ethanol. the pellets are dried for 2 hours or more in a vacuum dessicator before addition of 200 ul lysis buffer containing Proteinase K and overnight

incubation at 58° C. On the following day the Proteinase K is inactivated by a 10 minute incubation at 95° C. Any remaining debris is removed by a 10 minute centrifugation in the microfuge, and the supernatant is ready to use as a template source for a variety of molecular analyses.

3. **Collection of plasma, serum and urine:**

Plasma samples are collected into EDTA-containing collection tubes. After separation from the cellular component, the plasma are aliquoted to a freezing tube, labeled, and frozen at -20°C at the participating institution. These samples are batched and when several tubes have been collected, they are shipped on dry ice overnight to Georgetown University (Lombardi Cancer Center), where they are catalogued, kept at 4°C for short term storage and -70°C for long term storage. Frozen urine is shipped in batches to the Georgetown for processing and analysis.

4. **Training of data managers:**

On a regular basis, not less than once a year, a portion of the CALGB Clinical Research Associates workshop is devoted to instruction of the proper methods of obtaining and shipping the above specimens.

5. **Receipt of Specimens:**

Centers receiving specimens will electronically report to the CALGB database the receipt and condition of the specimen using standard CALGB procedures.

6. **Tracking of Patient Specimen Submission:**

The CALGB data management system tracks patients who are entered on CALGB protocols and plans to implement a system soon that will generate reminders to institutions that have entered patients on treatment protocols if the required specimens have not been received at the appropriate office or lab in a timely manner.

Use of the data from the Linked Registry: All uses for the information in the linked registry will be described in formal protocols that define the objectives, methodology, and statistical assumptions. These must be reviewed and approved by the Steering Committee. Letters are sent to the users setting out the agreement under which they use the registry. These were included in Appendix 3 of the progress report for year 2 of the project. Written proposals from the scientific community are considered if they do not compete with approved projects already underway, and are prioritized with respect to anticipated amount of tissue or resources consumed vs. the likely yield of important information. In assigning this priority to scientists who are not CALGB members we use the same scale that will be used for projects developed by CALGB members. In all cases emphasis is placed upon the level of innovation and the track-record of the

investigator with respect to peer review and publications. We plan to deliberately include projects, however, from young investigators without a track record, if they are endorsed by knowledgeable mentors and are innovative.

The availability of the Linked Registry is publicized through usual channels of scientific communication. In addition, the CALGB newsletter that is sent to many investigators outside the CALGB will be used as will news releases to "The Cancer Letter", and similar publications. Eventually, information about the CALGB Linked Registry will be available at the CALGB World Wide Web site.

B. Progress in Year 4.

Introduction: The progress reports for previous years mentioned that patient accrual to this study was far less than anticipated and described steps that were being taken to address this problem. During year one, it appeared that the availability of genetic counseling within CALGB institutions, a resource needed if the results of testing for familial cancer gene testing were to be made available to study subjects, was the principal stumbling block to adoption of the protocol at many CALGB institutions. We recognized this need during the design phases of the project and described it in our application. Beginning in the second year of the project we instituted a program intended to provide extensive training in the necessary genetic counseling skills. At that time, we anticipated that results of genetic testing would be available during year 4 of the project.

Despite the progress of the training program, the number of institutions approving the study remained far less than anticipated and it became clear during the second year of support that other aspects of the project also caused concern at our institutions. During this time, several articles appeared in the scientific and lay press calling attention to the potential risks involved in familial gene studies. Although these publications recommended that such testing should occur in the context of research trials of the sort this project represents, Institutional Review Boards (IRBs) were not willing to approve testing for familial cancer genes in the context of cooperative clinical trials. We were asked to assist in providing information addressing these concerns and amended the protocol to address the principal issues these committees raised about the project. Nevertheless, the accrual remained much lower than anticipated in the third year of the project.

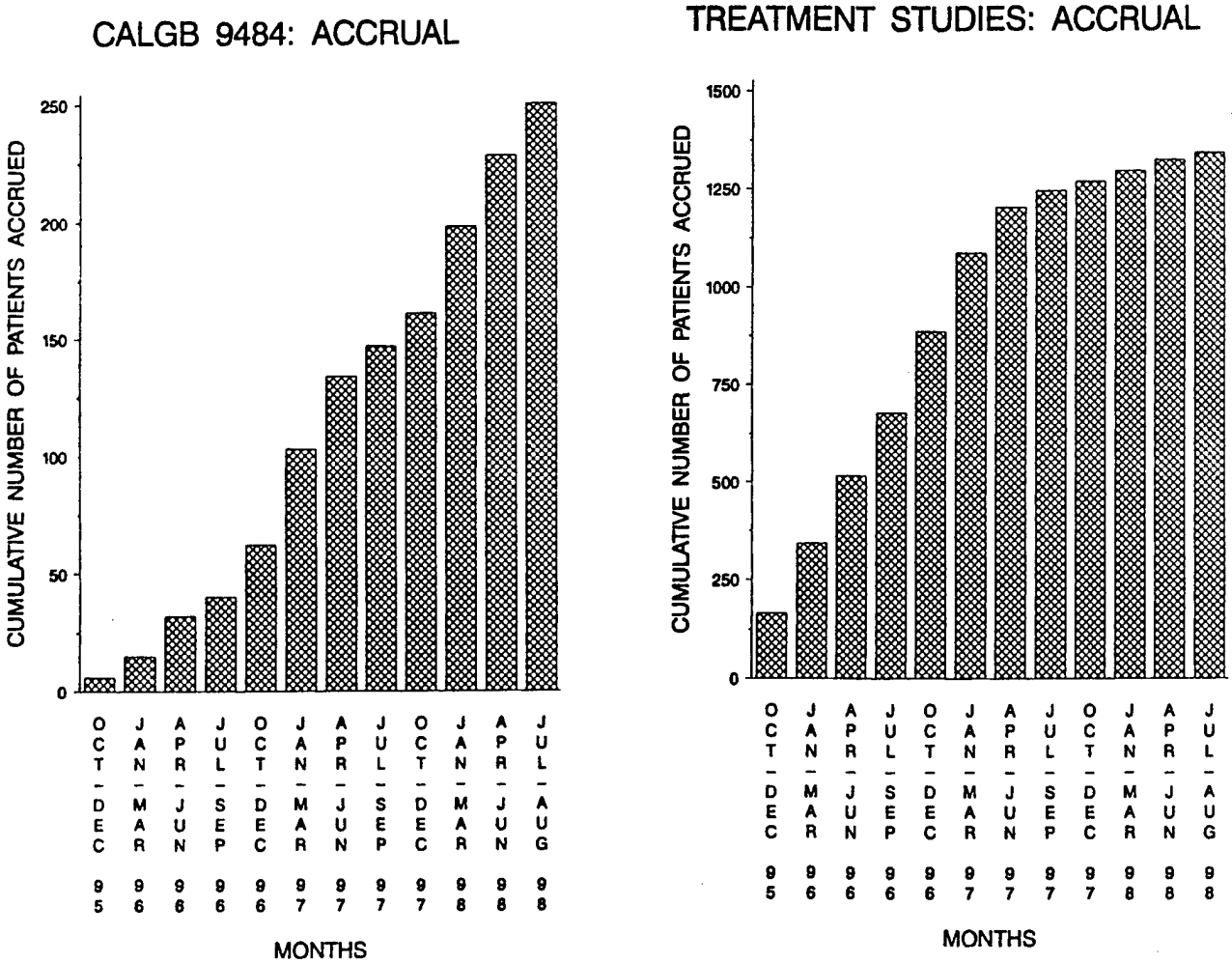
During the fourth year of the project, the difficulties in achieving the anticipated accrual were the subject of a poster presentation at the *Era of Hope* meeting sponsored by the Army Breast Cancer Research Program. Additional changes to the protocol and consent process designed to improve patient and institutional acceptability were described in our last progress report and have been implemented during the fourth year of the project. These are described more fully, below.

Apart from accrual, all other goals set for the project have been met. We have continued to assess the impact of the low accrual upon the types of research this project can support and have considered various alternative research projects. These are briefly described in the final section of this report. The pilot testing of the questionnaire has been completed, specimen submission has gone smoothly and a review of the forms submitted on patients entered to date has revealed no problems.

Patient Accrual and Revision of CALGB Protocol 9484 to Improve Accrual:

Information on patient accrual is displayed in figure 2. Here the number of patients entered on CALGB 9484 is compared to the number of patients entering CALGB treatment protocols over the period of the study. It is seen that the fraction of patients entering treatment studies who also participate in CALGB 9484 is increasing over time, presumably as a result of the various steps that have been taken to improve accrual.

Figure 2 - Accrual to CALGB treatment studies and to the "Linked Registry" (CALGB 9484) over the project period.



Most importantly, nearly all patients who have agreed to participate in CALGB 9484 have also agreed to provide a specimen for familial gene studies Since provision of such a specimen is not a requirement for participating in 9484, this indicates that most patients who are informed about the study and agree to participate are willing to have familial gene studies performed.

Protocol amendment:

In an attempt to improve accrual the original protocol was amended in 1996. The revised protocol contained the following changes:

1. Patients were no longer given the option of receiving the results of familial gene studies performed on their specimens. Such testing had become commercially available thereby obviating ethical issues that had led us to offer to provide test information, if desired by the patient, in the original study design. (See previous progress reports for the background leading to these decisions.) As a result of this change

a) there was no longer a requirement that the institution must have a genetic counseling program in place for the study patients,

b) confidentiality issues posed by the return of results of research genetic tests to the institution were avoided, and

c) since the research results would be located in the CALGB database at Duke University rather than in the records of about 200 institutions, the process of obtaining a Certificate of Confidentiality from the Department of Health and Human Services would be simplified.

Accrual to the amended protocol:

Despite these changes, the number of participating institutions and the number of patients entered into the study increased more slowly than anticipated during the second half of 1996 and the first half of 1997. With the impending closure of CALGB protocol 9344 in July 1997, the major breast cancer adjuvant study led by CALGB and the source of the majority of new CALGB breast cancer patients, the Steering Committee met June 2, 1997 in Chicago to consider further steps that could be taken to improve accrual.

Wording required in consent forms: The protocol covering the activities of the Registry, CALGB 9484, had been amended at the request of the investigators and institutions so that the consent form for investigational treatment and that for participation in the Registry were combined. This resulted in a significant increase in efficiency at our institutions. However, the Office for Protection from Research Risks (OPRR) of the NIH found that

language required by the Army concerning the donation of specimens was "exculpatory" and indicated that it would not approve the combined model consent form. The Steering Committee recommended that the Principal Investigator and his colleagues attempt to resolve this issue. Several phone calls and letters to the parties involved failed to eliminate the impasse and, as a result, the CALGB prepared its new adjuvant treatment protocol with two separate consent forms in order to satisfy a review by the parties funding the treatment and Registry functions respectively. This resulted in various inefficiencies at the institutional level.

Fortunately, during this same interval, under the leadership of the Breast Cancer National Action Plan and the National Cancer Institute, a simplified consent document was being drafted. Dr. McIntyre participated in the review of this and, with appropriate editing, the simplified consent document was approved by the Army. It should be noted that language previously required in the consent form and which institutions found troubling has been completely deleted in the revised form. The protocol amendment containing the simplified consent form was distributed to CALGB institutions in the spring of 1998. The amended and approved protocol is included as Appendix 1. There is an interval required for IRB review and approval at CALGB institutions and it may be too early to assess the impact of these further revisions of the protocol on institutional approval rates. So far, there is no major improvement in accrual.

Other Actions to Improve Patient Accrual:

1. Requirement that information on research subjects be maintained for 75 years by the federal government: We were informed during the review of the revised consent form for CALGB 9484 that since this project is viewed by the Army Research and Materiel Command as posing minimal risk to the patients there was no need to submit long term follow-up information on participants to the federal government. The consent form has been changed to reflect this.

2. Problems with submission of tissue blocks to our tissue repository in a state where state regulations had been interpreted as prohibiting this activity. A ruling from the New York State Department of Health that the CALGB Pathology Coordinating Office may act as a repository for such specimens was issued August 26, 1996. This eliminates the problem in that state and sets a precedent for other states where this issue could be raised.

3. Certificate of Confidentiality: A Certificate of Confidentiality covering this project was obtained from the Department of Health and Human Services in 1996.

Progress toward meeting Specific Technical Objectives:

a. **To modify questionnaires currently in use by CALGB investigators at the University of North Carolina, University of Minnesota and NIEHS to collect key family history and exposure data in a self-completed questionnaire.**

The self completed patient questionnaire contains items from the above sources and additional input from the team led by Dr. Fred Li at the Dana Farber Cancer Institute has occurred so as to yield a questionnaire that meets the broad needs of investigators. Under the leadership of Dr. Millikan and Ms. Cirrincione a draft self completed questionnaire was developed that addressed the needs of the patients and was capable of being interfaced with the CALGB Data Management System. Pilot testing in CALGB institutions during the early spring of 1995 revealed several problems which were corrected in a further draft that was tested in April. The final version is incorporated in CALGB protocol 9484 which was mailed to CALGB institutions on May 15, 1995 for activation.

The telephone interviews with study participants have gone well and with excellent patient cooperation. Because accrual has been less than anticipated during this period, telephone interviews have been carried out on all patients rather than the originally planned sample.

Because participants in the amended protocol will not receive information concerning familial gene status, study participants will no longer consist of two groups: those who wish and those who do not wish to know their status with respect to familial cancer genes. Thus portions of the original questionnaire dealing with the topic of the choice to receive information on gene carrier status will be no longer be relevant. The questionnaire has been modified accordingly and pilot testing of these modifications has been successful.

b. **To establish review procedures and criteria for selecting patients with a family cancer history for further study. Criteria will include, but are not limited to, having one or more first-degree relatives with breast cancer or having two or more relatives with breast, ovarian, or colon cancer.**

This technical objective was changed during our budget negotiations prior to activation of the project given the budget limitations. We will not allocate those with a family history of colon cancer into the group for the telephone interview. By so doing we will:

(i) enrich for BRCA1 and BRCA2 and potentially ataxia telangiectasia (AT) families, rather than diluting our efforts with potential mismatch repair (MMR) families,

(ii) avoid overlap with a proposed colon cancer susceptibility study supported by other funding

(iii) allow us to focus (as we should) on breast cancer screening and treatment issues, even though colon cancer is an important disease.

The purpose of developing the selection criteria is to yield a pool of individuals with a family history of breast cancer who will participate in an intensive telephone interview. This hour-long interview was developed with input, not only by investigators from this project, but in concert with others who have grants from the U.S. Army Research and Materiel Command to support related investigations. In addition, a control group of individuals without a family history of breast cancer who are under treatment on CALGB breast cancer protocols is included, as noted above, for comparison purposes.

c. **To develop a telephone interview with patients identified for further study that will expand on the screening data collected, obtain information that will facilitate validation of cancer reported, and locate selected siblings for inclusion in the database. The study will obtain exposure information from affected and unaffected first-degree relatives of patients with a family history of cancer.**

The telephone interviews are proceeding well and there are no problems with this aspect of the study.

As noted above, the interviewing of family members was eliminated from the project prior to study activation as a result of the need to reduce the budget.

d. **To collect fixed breast tissue from patients and germ-line DNA, plasma, and urine on the above patients and family members.**

CALGB 9484 covering the submission of tissues and specimens listed above, was mailed to CALGB institutions on May 15, 1995. As of September, 1998 the protocol has been approved by the IRBs in 99 of 229 CALGB institutions. This represents an improvement over 1997 when only 78 of 199 institutions had approved of the protocol.

e. **To review and confirm the histopathological diagnosis of breast cancer on submitted tissue.**

This activity is proceeding without any problems.

Infrastructure and Policy Development:

Overview:

The Pathology Coordinating Office has developed an integrated coordination and communication network through the Tissue Resource Coordinating Committee for the systematic collection, archiving, surveillance, quality control and quality assurance for the acquisition and processing of the fixed, paraffin tissue blocks for this study. The appointment of a tissue bank coordinator, who also serves as the CALGB Committee Vice Chair and Tissue Bank Coordinator for solid tumor correlative science studies will facilitate and expedite this integration, interfacing with database management, maintaining appropriate quality control and quality assurance procedures for the storage and processing of tissues, and developing policies to respond to institutional pathology concerns of tissue banking. In addition, we have identified coordinating/contact pathologists at each of our main and affiliate institutions to expedite case accessioning of paraffin blocks and to establish a network of communication for responding to mutual concerns and problems that may develop during the course of the study (additional efforts to integrate pathology participation are discussed section 3). The following sections describe pathology policy that we have developed for tissue banking (see Section A-1 and Appendix 6 of the progress report for year 2), and detailed procedures for processing to ensure quality control and quality assurance as well as steps taken to avoid depletion of the block (Appendix 7 of the progress report for year 2).

Pathology policy development for tissue banking:

Although tissue acquisition for this study commenced October, 1995, the Pathology Coordinating Office has had prior experience collecting blocks as a mandatory requirement for four breast cancer clinical trials now active in the CALGB. Because of varying certification and licensing requirements placed at the federal, state and professional society level concerning retention of blocks by institutional surgical pathology laboratories it is not always clear whether all or simply representative tissue blocks are required to remain on file by a pathology laboratory. Some hospital policies prohibit release of an entire block for storage, but will allow cut sections to be stored. Many hospitals are willing to release blocks if they can be assured of accessibility to representative material for any future medical-legal need. In order to address these concerns, and offer alternatives for those hospitals whose policies prohibit release of an entire block for storage, we have developed a Tissue Bank policy for this study (Appendix 6 of the progress report for year 2).

Quality control and quality assurance of tissue blocks/sections:

Several precautions are taken to ensure that appropriate processing is performed to accommodate a variety of laboratory uses. High quality sections that are representative of the histopathologic diagnosis of breast cancer are required. For example, to reduce possible DNA contamination for molecular assays the following precautions are taken: gloves are worn by the histotechnician, the disposable blade is wiped down with 10% bleach, followed by 70% alcohol between each block unless a new blade is used; the water bath surface is cleaned between each block, clean forceps are used for each block. In addition, all thick, 10 micron sections cut for molecular assays are placed on uncoated slides (to facilitate scraping) and are stored at 4 degrees. All intact blocks are stored at 4 degrees to minimize antigen deterioration. Thin sections cut for immunohistochemistry are stored at a minimum of 4 degrees (preferably -70°C) and are placed on coated slides (to avoid tissue detachment during assay). H & E sections are cut at different levels throughout the block to ensure that representative tissue is being used for a particular assay. These procedures also address the steps to be taken when minimal tissue is available from the block. This ensures that tissue will not be exhausted in these blocks. A detailed procedure for processing of tissue sections for molecular, immunohistochemical and flow cytometric assays was offered in Appendix 7 of the progress report for year 2.

Efforts to Integrate Pathologist Participation in this Study:

The institutional pathologist is a critical link for accessing representative tissue for laboratory studies. However, in the cooperative group setting, the pathologist has often not participated in breast cancer studies except in the submission of tumor blocks to the Pathology Coordinating Office. In 1997, Dr. Ira Bleiwess of Mount Sinai Hospital was named as the coordinating pathologist for breast cancer studies and was named to the Steering Committee for the project. In an effort to enhance integration of pathologists into the cooperative research process for breast cancer clinical trials and correlative science studies, Pathology Workshops are held at CALGB meetings to disseminate information regarding breast cancer studies, to discuss the active role that pathologists can play in these studies and provide a forum for problem resolution with respect to accession and tissue banking. The concept of these workshops and pathology integration in cooperation is fully supported by the College of American Pathology.

f. To integrate information about specimen receipt, specimen availability, and laboratory testing results with the CALGB database and to prioritize use of this information.

This activity is a major goal for year 4 of this project.

g. **To modify the CALGB database and data handling procedures at the CALGB Statistical and Data Management Center at Duke University, so as to efficiently capture and record information from the registry, and to furnish it to users.**

Under the leadership of Ms. Donna Hollis and Gloria Broadwater, the first half of the above objective has been met. As information concerning these studies is gathered, the second portion of this task will be performed, namely the integration of the information with clinical characteristics, response to treatment and other endpoints.

Information from the telephone interviews is being recorded and then entered by a subcontractor at the University of North Carolina. Cleaned and verified data on the first 200 patients will be ready for transfer to the CALGB Data Management Center around October 1, 1998.

Further thinking about the research design has indicated that a goal of furnishing the database information to users is inappropriate. Instead, the results of laboratory and other investigations will reside in the database and will be accessed by CALGB statisticians in order to address hypotheses offered by all investigators participating with CALGB in this project.

h. **To augment resources at CALGB institutions in order to procure the above described information and specimens.**

Payments to institutions to cover the costs of selecting or obtaining specimens has begun. Because accrual has been slower than originally anticipated, the cost to the project for reimbursement of institutional expenses has been less than originally budgeted.

III. SUMMARY

A. <u>Conclusions:</u>

1. CALGB Protocol 9484, providing the basis for specimen and data collection for a Linked Breast Cancer Registry, has been further amended to augment patient accrual. The language previously required by the sponsor which institutions found problematic has been removed. Despite the improvement in accrual that has resulted, patient entries to the Registry are still far less than originally anticipated. Possible reasons for this are offered in the text of the progress report. In addition, certain new research initiatives that can be accomplished with the smaller number of patients available within the registry are summarized.

2. Problems concerning the nature and process of informed consent for studies of familial breast cancer genes have been addressed in a publication by Millikan, et al. based upon results from the project: Genetic Testing in Breast Cancer Cooperative Clinical Trials: Barriers and Opportunities[30] (Appendix 2)

3. The procedures used for the telephone interview have been developed, pilot tested, revised and implemented. The responses from the patients to the telephone interview have been uniformly positive.

4. The DNA extraction apparatus has been purchased, installed, and is in use at the University of North Carolina, Chapel Hill. The freezer for urine and plasma samples that was purchased at the Dana Farber Cancer Institute, Boston has been moved to Georgetown University where Dr. Hayes, the subcontractor for this portion of the project, assumed a faculty position. Specimens of plasma and urine are now being shipped to that location.

5. Four workshops for CALGB physicians, nurses, data coordinators and genetics counselors have been held since 1996. These provide training in order to assist in recruiting patients to the study. The next 3 hour workshop will be held at the meeting of the CALGB on November 20, 1998. The workshop will include an update on recent developments in cancer genetics by Dr. Olopade, cancer risk assessment and cancer genetic counseling by Ms. Cummings, breast/ovarian syndromes and genetic testing by Dr. Woods, quantitative genetics - the Berry/Parmigianni model by Dr. Berry, and case studies/CALGB protocols by Drs. Berry and McIntyre

6. *Changes in Project Staff:*

   Previous changes in staff have been described in earlier progress reports.

   In 1998, Dr. Carolyn Compton replaced Dr. Maurice Barcos as the Director of the CALGB Pathology Office. Her biographical sketch is attached as Appendix 3. As a result, it is planned that the activities of this office will move from Roswell Park Cancer Institute to the Massachusetts General Hospital during 1999. There will be no change in the research procedures as a result of this move, nor will there be any change in the cost of the research. Approval for the transfer of the subcontract covering this activity of the project has been given by the sponsor.

B. <u>Changes Resulting from Experience in Year 4. Problems and Corrective Actions.</u>

As in year 3 the major problem during year 4 has been the continued slower than anticipated accrual to CALGB 9484. The initial version of our protocol was developed as a consensus among those with expertise with regard to regulations concerning use of human subjects and cancer advocates. Despite this input, there has been much slower than expected approval of the protocol at our

institutions as described above. Although our project was conceived and designed to minimize the risks involved in this kind of research, the appearance of cautionary articles for the lay and scientific community [31] resulted in a changed climate for the institutional review of this project. By August 31, 1998 the protocol has been approved in only 43% of CALGB institutions. The substantial changes in the consent form made during 1998 described in previous sections may yet result in larger participation.

The Steering Committee is gratified that a one year no cost extension of the project has been approved by the Army. Because of the slower accrual, there remain sufficient funds to continue the project at our current level of activity for the additional year. This will allow the recruitment of an additional 150 patients or more to the project and result in a total sample of about 350 patients on whom we have the specimens and detailed information collected by the project.

As the Registry was originally conceived, some proposals for its use entailed analyses from large numbers of patients (more than 1,000). Other research could be successfully completed with the number of specimens likely to result from the Registry at its current rate of accrual. These were reviewed and additional projects were discussed. Some of the projects under consideration by the Steering Committee are listed below:

1. Case-case (case series) comparison: Risk factors for breast cancer in patients with a family history versus in women without a family history.

2. Prevalence of patients with a positive family history and other characteristics of women in clinical trials. We do not know how representative clinical trial patients are versus breast cancer patients in general in terms of family history and other factors.

3. Evaluate self administered questionnaires: Are they as valid as a more detailed family history obtained via phone interview?

4. Samples are requested to test hypotheses developed by Holland, et al. These investigators using PCR technology have reported finding a 660 base pair sequence, unique in the gene bank for a portion of the envelope gene of the murine mammary tumor virus (MMTV) in 38% of breast cancer specimens from American women. The sequence is not found in other tumors, normal tissues, or tissues other than breast cancer of the affected patients. Archival specimens confirm this finding, with 37% positive using a 250 base pair sequence within the 660 base pairs.[32]

Based on this preliminary data, the investigators hypothesize:

a) Breast cancer in American women associated with the sequences homologous to MMTV is different in its behavior from breast cancer which is negative by PCR.

b) Breast cancer arising during pregnancy or lactation is more likely to be associated with the sequences (80% in the preliminary data).

c) Breast cancer positive for MMTV env-like sequences is likely to occur at an earlier age than negative tumors.

d) Breast cancer specimens are likely to be associated with increased frequency of axillary nodal metastasis.

e) Metastatic axillary lymph nodes containing breast cancer from a primary neoplasm that is positive by PCR would also be positive, and that metastatic axillary lymph nodes of breast cancers negative by PCR will be negative.

7. Polymorphisms in DNA repair genes and response to chemotherapy: Dr. Harvey Mohrenweiser, Human Genome Center, Lawrence Livermore National Laboratory, has proposed a collaboration using the Registry. He has recently identified common variants in genes involved in DNA repair. These variants could provide important prognostic information for patients undergoing adjuvant chemotherapy or radiation therapy. The nucleotide excision repair (NER) pathway removes bulky adducts from DNA, including those produced by a wide array of chemotherapeutic drugs. Deficiencies in NER could increase responsiveness to chemotherapeutic drugs, since effective removal of bifunctional DNA adducts leads to drug resistance[33,34]. A second DNA repair mechanism, the double-strand break (DSB) - recombination pathway, is involved in repair of radiation-induced DNA damage[35]. Patients with suboptimal repair of radiation-induced DNA damage are at increased risk for breast cancer[36,37,38,39,40] and might be at increased risk for recurrence and/or side-effects following radiotherapy. The existence of DNA repair genes with common, low penetrant alleles has been hypothesized[33] but none have been identified to date. Identification of such genes would be a considerable advance, and could lead to more effective uses of chemotherapy and radiotherapy tailored to the responsiveness of individual patients.

Preliminary data.

Dr. Mohrenweiser has identified several common variants (allele frequencies of 10% or greater) in genes involved in both NER and DSB repair pathways. Variants in NER include alterations in ERRC1, and

variants in DSB repair include alterations in XRCC1, XRCC3 and RAD51. The role of these genes in breast cancer has not been examined to date, but NER and DSB repair are likely to be relevant for both etiology and progression of breast cancer. Recently, the C-terminus of BRCA1 was shown to contain a region of homology with XRCC1 and other DNA repair proteins[41] and RAD51 binds to both BRCA1[42] and BRCA2[43].

Proposed project.

We plan to genotype participants in the Specialized Registry for polymorphisms in NER and DSB repair genes. We will investigate two types of interactions:

(i) By combining NER/DSB genotype information with treatment information, we can examine gene - environment interaction. We hypothesize that patients with NER defects will respond better to high dose chemotherapy, and patients with DSB defects will be at increased risk for recurrence following radiotherapy.

(ii) By combining NER/DSB genotype information with assessment of germline alterations in BRCA1 and BRCA2, we can address gene-gene interactions. It is possible that inheritance of rare mutations in BRCA1/2, combined with inheritance of common alterations in NER and/or DSB repair genes, combines to increase or decrease therapeutic response.

In this collaboration Dr. Douglas Bell, National Institute for Environmental Health Sciences, will supervise high-throughput genotyping of DNA repair gene variants in samples from patients in the Specialized Registry. As part of previously funded projects in the University of North Carolina Specialized Program of Research Excellence (SPORE) in breast cancer, we are already conducting genotyping of DNA repair variants in Dr. Bell's laboratory, and the specimens from the Specialized Registry will be analyzed at no cost.

Retention of Tissue Blocks: An unexpected number of institutions have requested that the blocks submitted on 9484 be returned immediately after sections have been taken and have cited various regulatory or legal requirements as the reason for these requests. In order to resolve this problem we have taken two courses of action. We try to convince those making this request that it is reasonable for us to have custody of their blocks as long as we demonstrate that we can return them to the institution within one business day of a request for their return. Second, we maintain paraffin sections at low temperatures in order to preserve antigens. In addition, we indicate, on the slide, the date the sections were cut. We are also conducting time-course experiments to optimize storage conditions for detection by new antibodies as they become available for use. This may stabilize antigens that have been shown to deteriorate in sections maintained at the higher temperature.

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CANCER AND LEUKEMIA GROUP B

MEMORANDUM

To: Principal Investigators, CCOP Responsible Investigators, Disease and Modality Chairs, Executive Committee, Data Management Center, Statistical Center, QARC

From: Kathleen S. Karas, Senior Protocol Editor

Subject: **CALGB 9484: Forms C-383, C-384, C-449, and C-490**

Date: June 15, 1998

Attached please find revised versions of Forms C-383, C-384 and C-449 for CALGB 9484. Please replace previous versions of these forms with those attached. In addition, please replace Form C-350 in the appendix with the attached Form C-490, Tracking Form (Tissue Blocks).

Please note that urine samples are not being collected at this time; you will be notified when urine collection is to commence.

If you have questions regarding these forms, please contact Dana McDonald, Data Coordinator, at 919-286-0045, x235.

cc: O. Ross McIntyre, M.D., D. McDonald

Update #2
5/15/98

CANCER AND LEUKEMIA GROUP B

PROTOCOL UPDATE TO CALGB 9484

LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

__X__ **Revision** __X__ **Amendment** ___ **Status Change**

__X__ Change of participants/coordinator (s) +/-
__X__ Editorial, administrative changes
_____ Scientific changes (IRB approval)
_____ Therapy changes (IRB approval)
_____ Eligibility changes (IRB approval)
__X__ Informed Consent changes (IRB approval)
_____ Other:

___ Activation
___ Closure
___ Partial Closure
___ Temporary Closure
___ Reactivation

Cover page: Dana McDonald replaces Laura Gross as data coordinator. Phone and fax numbers for Dr. Berry have been updated. CALGB 9741 has been added to the list of studies to which CALGB 9484 is a companion.

Section 4.1: CALGB 9741 has been added to the list of eligible studies.

Section 4.2: The statement that patients must initial the consent form has been replaced with "patients must indicate their agreement by circling yes or no on the consent form".

Section 5.0 Registration: The question "Does patient release or retain rights to specimens" has been removed.

Section 8.5 Shipment billing: Pre-printed Federal Express labels are no longer available. Instructions should continue to use the Federal Express account number provided by the Central Office when filling out shipment labels.

Section 10.0 Model Consent: A new model consent form is provided which may be used in place of the previously issued consent form. This simplified consent is based on a model for tissue procurement developed by the National Breast Cancer Coalition with input from various agencies, including the National Cancer Institute, and has been approved by the Department of Defense for use with this study. This model may either be combined with the treatment consent or used as a separate document at the discretion of the participating institution.

Please note that urine should NOT be collected or shipped at this time. You will be notified when urine collection should begin.

Replacement pages: Cover page, p 3-4, 9-10, 14-16.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

cc: O. R. McIntyre, M.D., D. F. Hayes, M.D., D. Sandler, Ph.D., B. Smith, M.D., D. Berry, Ph.D., R. Millikan, DVM, Ph.D., D. McDonald

CANCER AND LEUKEMIA GROUP B

MEMORANDUM

To: Principal Investigators, CCOP Responsible Investigators, Disease and Modality Chairs, Executive Committee, Data Management Center, Statistical Center, QARC

From: Kathleen S. Karas, Protocol Editor

Subject: **CALGB 9484: Forms C-383, C-384, C-449**

Date: March 15, 1997

Attached please find revised versions of Forms C-383 and C-384 for CALGB 9484. Please replace previous versions of these forms with those attached. In addition, Form C-449, Urine Sample Tracking Form, is provided. **Urine samples are not being collected at this time; you will be notified when urine collection is to commence.** Please insert Form C-449 in the appendices of CALGB 9484 for use once urine collection is initiated.

If you have questions regarding these forms, please contact Laura Gross, Data Coordinator, at 919-286-0045, x235.

cc: D. F. Hayes, M.D., D. Berry, Ph.D., C. Cirrincione, L. Gross

CANCER AND LEUKEMIA GROUP B

MEMORANDUM

To: Principal Investigators, CCOP Responsible Investigators, Disease and Modality Chairs, Executive Committee, Data Management Center, Statistical Center, QARC

From: Kathleen S. Karas, Protocol Editor

Subject: **CALGB 9484: Urine Specimens, Eligibility**

Date: November 15, 1996

IMPORTANT NOTICE

PLEASE DO NOT COLLECT OR SHIP URINE SPECIMENS FOR CALGB 9484 UNTIL FURTHER NOTICE.

Update #1 to CALGB 9484 issued 10/15/96 indicated that urine collection and shipment should begin. However, due to difficulties encountered in the processing of specimens, **please do NOT collect or ship urine specimens until notified** (via e-mail broadcast and/or protocol mailing notice). We expect these difficulties to be resolved shortly, and appreciate your patience in this matter. If you have any questions, please contact me (773-702-9674, kkaras@midway.uchicago.edu) or Dr. Hayes (202-687-2103, hayesdf@gunet.georgetown.edu).

PATIENT ELIGIBILITY FOR CALGB 8861, *Monitoring CA 15-3 Antigen During and After Adjuvant Therapy for Stage II, Node Positive Breast CA:*

Please note that if 9484 is active at your institution, you should **not** be entering a patient on both 8861 and 9484. New patients should be entered on 9484; only patients previously entered on 8861 (prior to activation of 9484 at your institution) should continue to have their samples submitted under 8861. If you have any questions, please contact me or Dr. Hayes.

cc: D. F. Hayes, M.D., D. Berry, Ph.D., C. Cirrincione, L. Gross

CANCER AND LEUKEMIA GROUP B

PROTOCOL UPDATE TO CALGB 9484

LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

__X__ **Revision** __X__ **Amendment** ____ **Status Change**

__X__ Change of participants/coordinator (s) +/-
__X__ Editorial, administrative changes
__X__ Scientific changes (IRB approval)
_____ Therapy changes (IRB approval)
_____ Eligibility changes (IRB approval)
__X__ Informed Consent changed (IRB approval)
_____ Other:

____ Activation
____ Closure
____ Partial Closure
____ Temporary Closure
____ Reactivation

Due to the extensive changes made to this study, a replacement document is being issued at this time. Please discard the previous version of this protocol, including the model consent form. The appendices, however, should be retained, except for the following: replace the CALGB Detailed Family History and Epidemiology Telephone Interview in Appendix II with the updated version in this update, and add new Appendix IV, DHHS Confidentiality Certificate.

Note: The C-449 form for urine collection is not included in this mailing but will be issued in a subsequent mailing. If you need a C-449 form in the interim, please contact the CALGB Data Management Center, 919-286-0045, x221.

SUMMARY OF REVISIONS:

Address and phone numbers have been updated for Dr. McIntyre, Study Chair, Breast Committee Chair, Data Coordinator, and Dr. Hayes. ***PLEASE NOTE THAT ALL URINE AND BLOOD SHIPMENTS TO DR. HAYES SHOULD BE SENT TO LOMBARDI CANCER CENTER, NOT DANA FARBER CANCER INSTITUTE. EFFECTIVE WITH THIS UPDATE, URINE COLLECTION SHOULD BEGIN AS SPECIFIED IN THE PROTOCOL.***

The telephone area code for the Central Office has been changed; the fax number, however, remains the same.

Specimen procurement and shipping instructions have been clarified throughout the protocol.

The Department of Health and Human Services has issued a Confidentiality Certificate for this project; a copy is included as Appendix IV.

SUMMARY OF AMENDMENTS

Test results will no longer be provided to patients or their physicians. The tests conducted by the CALGB are intended for research, not diagnostic, purposes. Commercial tests are now available for those patients who wish to pursue this option after consultation with their physician. Since the results of research tests will no longer be provided to the institution, the requirement for comprehensive genetic counseling services has been dropped.

All references to registration of family members and studies of family members have been deleted, as these studies will not be pursued at this time.

There is no longer a free-standing consent form for 9484. Instead, the essential elements of consent for 9484 have been incorporated into the treatment protocol consent forms. The model consent sections are included in this protocol for reference only. Please see amendments dated 10/15/96 for protocols 9082, 9342, 9343, and 9344 and submit these revised treatment protocol consent forms to your IRB. Patients will be presented with all options included in the revised treatment consent form: collection of tissue, blood, urine, completion of questionnaires, and the separate section regarding the use of specimens to study heritable genes. Patients who agree to collection of tissue, blood, urine and the completion of questionnaires must initial these items within the treatment consent form as directed; patients who agree to have their specimens studied for heritable genes must sign the section of the treatment consent form entitled "Consent for Studies of Heritable (Familial) Cancer Genes". Registration to 9484 for those patients agreeing to these additional items should take place simultaneously with registration to the treatment protocol. Patients who agree to have their specimens collected, but refuse to have them studied for heritable genes, may still be entered on 9484. Questions regarding eligibility should be directed to the study chair, Dr. McIntyre, or to the Central Office (contact Kathleen Karas, protocol editor.)

This update contains Cover page through page 16, an updated CALGB Detailed Family History and Exposure Telephone Interview (Appendix II), and Appendix IV, DHHS Confidentiality Certificate.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

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cc: O. R. McIntyre, M.D., L. Norton, M.D., D. F. Hayes, M.D., D. Sandler, Ph.D., M. Barcos, M.D., L. Schnaper, M.D., D. Berry, Ph.D., L. Dressler, M.A., R. Millikan, DVM, Ph.D., L. Gross

Activation: June 15, 1995

CANCER AND LEUKEMIA GROUP B

LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

CALGB 9484

Companion to CALGB 9082, 9342, 9343, 9344, 9741

Study Chair
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DMMcDonald@elephant.mc.duke.edu

Protocol Editor
Kathleen S. Karas
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kkaras@midway.uchicago.edu

For questions regarding submission of tissue samples, contact:

Maurice Barcos, M.D.
CALGB Central Pathology Office
Roswell Park Cancer Institute
Department of Pathology
Elm at Carlton
Buffalo, New York 14263
Phone: (716) 845-4443 Fax: (716) 845-8077
calgbpath@sc3102.med.buffalo.edu

For questions regarding submission of whole blood samples, contact:

Lynn Dressler, M.A.
University of North Carolina
Medical Oncology Division
CB #7295 Lineberger Cancer Research Center
Chapel Hill, NC 27599-7295
Phone: (919) 966-0196 Fax: (919) 966-4244
dressler@med.unc.edu

For questions regarding submission of plasma and urine samples, contact:

Daniel F. Hayes, M.D.
Lombardi Cancer Center
Room E504
Research Building
3970 Reservoir Road, NW
Washington, DC 20007
Phone: 202-687-2103 Fax: 202-687-4429
hayesdf@gunet.georgetown.edu

For questions regarding forms, contact:

Dana McDonald
Data Coordinator
CALGB Data Management Center
First Union Plaza, Suite 340
2200 West Main Street
Durham, NC 27705
Tel: 919-286-0045, x235 Fax: 919-286-1142
DMMcDonald@ccstat.mc.duke.edu

For administrative issues, contact:

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TABLE OF CONTENTS

1.0 INTRODUCTION

This project involves the collection of tumor specimens, genomic DNA, and information concerning medical, reproductive, exposure and family history from patients with breast cancer. The purpose is to create a library in which clinical information on groups of uniformly staged and treated patients on CALGB protocols is located within a structure that also contains patient personal, family, and environmental exposure history, specimens from patients, and data from molecular and other laboratory studies. In contrast to a population-based tumor registry, it offers an internally cohesive group of patients with well-defined disease, treatment and follow-up. It will be possible to draw scientifically valid conclusions from this group by looking for interactions between treatment and factors such as genomic susceptibility and acquired somatic alterations.[1]

We have termed this resource a "specialized registry". The specimens (breast cancer tissue, plasma, urine, or in some cases, DNA) will be made available to qualified investigators who will conduct a variety of research projects that test laboratory-based, psycho-social or epidemiological hypotheses. These investigators will be supported by peer-reviewed grants and other mechanisms, and the studies will be done at no charge to patients. Laboratory results will be forwarded to the CALGB database where CALGB statisticians will be responsible for all analyses. All information resulting from these studies will reside in the CALGB database and all patient identifiers will remain confidential within the CALGB Data Management Center.

Population-based studies are not included at this time: with all of the ethical and legal ramifications inherent in population-based genetic studies, we feel that this type of study should come later when specific hypotheses are more fully formed and after we have established the scientific and psycho-social framework for communicating this type of information to the general public.

Ethical and legal issues relating to studies of heritable genes, and submission of tissue: Based upon policies adopted by the CALGB concerning studies of heritable cancer genes, a separate prospective informed consent for genomic DNA submission, as well as consent for participation in the other components represented, is required. These consent documents are incorporated into the consent documents for each relevant treatment protocol. Consent to participate in the specialized registry must be obtained at the time the patient enters the treatment study.

With respect to submission of fixed tissue blocks after diagnosis has been established at the local institution, there are a number of unresolved and sometimes conflicting issues that are currently being addressed by appropriate bodies. The "ownership" of the tissue blocks is felt by some to have been conveyed to the institution by the wording of the usual consent for surgery, but this is disputed by others who feel that, for the purposes represented by the studies to be performed via this protocol, the patient retains rights to the tissue. More particularly, the view has been expressed that the patient may have an enforceable privacy interest when studies are done on tissue that is linked in some manner to them.[3] We believe that the consent for the specialized registry included in each relevant treatment consent form specifies conditions in which the patient's right to privacy is not subjected to a new risk with each new use of the registry. State laws, the American College of Pathology, the Joint Commission on the Accreditation of Health Care Facilities, and the Clinical Laboratory Improvement Act (CLIA) may have requirements concerning retention of diagnostic tissue at the local institution, and it remains to be determined whether it is permissible under these policies to place the tissue in the custody of other approved parties. Finally, there are divergencies of opinion between the U.S. Army Medical Research and Materiel Command and the Office of Protection from Research Risks, National Institutes of Health, concerning a requirement that specimens collected with

funding from the Department of Defense become the property of the U.S. Government. Certain of these may require establishment of legal precedent for their resolution. Institutions with concerns about this possibly conflicting positions may wish to contact Dr. Maurice Barcos, Director of the CALGB Pathology Coordination Office, for additional information about the procedures that CALGB has established to ensure that fixed breast tissue remains available for return to the institution, if required.

2.0 OBJECTIVES

1. To collect formalin-fixed, paraffin-embedded (FFPE) breast tissue for in situ studies and extraction of somatic DNA and peripheral blood for extraction of germline DNA, also plasma and urine from patients with breast cancer entered on CALGB breast cancer treatment protocols.

2. To review and confirm the histopathological diagnosis of breast cancer on submitted tissue.

3. To gather key family, endocrine and reproductive history, and exposure data on the above patients.

4. To prepare and submit the above specimens to approved investigators who will perform various laboratory studies on them and provide the results to the CALGB database for correlation with clinical data and patient outcome.

5. To analyze the data resulting from the above activities in order to seek new knowledge about etiology and progression of breast cancer.

3.0 STATISTICAL CONSIDERATIONS

A Steering Committee is responsible for approving each individual project using the resources of the specialized registry. Each individual project submitted for review will contain a statistical section detailing the hypothesis and the estimated powers required in the proposed analyses. Flexibility is essential since the alternative hypothesis will vary from one project to the next. If the alternative hypothesis is close to the null, then a large number of patients will be required. A major element in the Steering Committee's review of the proposal will be whether the hypothesis may be adequately tested given the current resources of the registry.

Many of the proposals that we expect to receive will concern analyses of subgroups of patients within the registry. These would be conducted by evaluating an ordered list of scientific hypotheses using sequential statistical tests and would facilitate an early decision on whether a new hypothesis was worth further investigation, while avoiding wasting too much biological material on testing hypotheses that may eventually prove unfruitful. This method will also help to distinguish between a "multitude of hypotheses".[4] The value of the registry to the investigators will be enhanced if it is sufficiently large to allow them to test their hypotheses on subgroups of sufficient size so that adequate power is obtained to detect the differences which are sought. For this reason, the larger the number of patients represented in the specialized registry, the more useful the registry will be. It is anticipated that the alternative hypothesis will dictate power, and allocation of resources will proceed sequentially. There is a wealth of material on case only analyses, in which comparisons of cases only (no controls) are used to evaluate gene-environment interactions.[5] We have planned for a registry of up to 5,000 individuals but this number may be adjusted upwards or downwards without amending the protocol depending upon the experience with the various users and the ability to secure funds to operate the registry.

4.0 ELIGIBILITY CRITERIA

4.1 The patient must be enrolled on a CALGB breast treatment protocol. Those protocols from which patients may be entered are listed below. This list will be modified in updates (revisions) to this protocol to include additional CALGB adjuvant or metastatic breast cancer treatment protocols that are activated during the funding period.

9082 A Randomized, Comparative Study Of High Dose CPA/cDDP/BCNU and ABMS Versus Standard Dose CPA/cDDP/BCNU as Consolidation to Adjuvant CAF for Patients with Operable Stage II or Stage III Breast Cancer Involving ≥ 10 Axillary Lymph Nodes

9342 A Phase III Study of Taxol at Three Dose Levels in the Treatment of Patients with Metastatic Breast Cancer

9343 Evaluation Of Lumpectomy, Tamoxifen, and Irradiation of the Breast Compared with Lumpectomy Plus Tamoxifen in Women 70 Years of Age or Older Who Have Carcinoma of the Breast that is Less Than or Equal to 4cm and Clinically Negative Axillary Nodes: A Phase III Study

9344 Doxorubicin Dose Escalation, With Or Without Taxol, As Part Of The CA Adjuvant Chemotherapy Regimen For Node Positive Breast Cancer: A Phase III Intergroup Study

9741 A Randomized Phase III Trial of Sequential Chemotherapy Using Doxorubicin, Paclitaxel, and Cyclophosphamide or Concurrent Doxorubicin and Cyclophosphamide Followed by Paclitaxel at 14 or 21 Day Intervals in Women with Node Positive Stage II/IIIA Breast Cancer

4.2 Patients must indicate their agreement by circling yes or no on the consent form to have their archived tissue blocks, (including somatic DNA but excluding analyses of germline genetic characteristics on associated normal tissues), plasma, and urine submitted for study and to participate in collection of family, exposure and endocrine history questionnaires. Note: If the patient also consents to participate in genomic studies, cells for genomic DNA must be obtained prior to the first radiation or chemotherapy treatment.

5.0 REGISTRATION

Registration will be accepted through the Main Institution only. Confirm eligibility criteria (Sec 4.0). Call the CALGB Registrar (919-286-4704, Monday-Friday, 9 am-5 pm Eastern Time) with the following information:

Your name
Study #
Institution #
Treating Physician
Patient' s Social Security #
Patient' s Name, I.D.#
Patient's Address and Phone Number
Signed Informed Consent (Date)
Type of consent signed: Genomic studies, Non-genomic studies
Race, Sex, Date of Birth
Zip code of residence
Method of payment
Diagnosis, Date of Diagnosis
Eligibility Criteria met (Sec. 4.0) (yes, no)
List CALGB treatment protocol
Date of most recent Institutional Review Board approval (<1 year)

6.0 REQUIRED DATA

6.1 Submit data forms and specimens according to protocol requirements for all patients registered on CALGB 9484 who receive treatment on an appropriate CALGB breast treatment protocol.

6.2 CALGB institutions should submit specimens along with their corresponding pathology/specimen submission forms to the appropriate CALGB laboratory for storage, as indicated below. If tissue block will not be submitted for a patient, the institution should submit the CALGB Pathology Routing Form (C-350) indicating the reason for nonsubmission along with a letter from the institutional pathologist explaining the reason for nonsubmission.

Copies of these forms are included in this appendix.

6.2.1 Submit **tissue block** (or letter stating why tissue block will not be submitted), surgical path report and **original** C-350 form to:

Maurice Barcos, MD, PhD
CALGB Pathology Coordinating Office
Roswell Park Cancer Institute
Elm & Carlton Streets
Buffalo, NY 14263-0001

and a copy of C-350 form to the CALGB DMC; keep a copy for your records.

6.2.2 Submit **whole blood** specimens with **original** C-383 form to: **(NOTE: PATIENT MUST HAVE SIGNED CONSENT FOR STUDIES OF HERITABLE GENES)**

Qing Yang/Daynice Skeen/Lynn Dressler
UNC DNA Extraction Laboratory
University of North Carolina
CB #7295 Lineberger Cancer Research Center
Mason Farm Road, Room 350
Chapel Hill, NC 27599-7295

and a copy of C-383 form to CALGB DMC; keep a copy for your records.

6.2.3 Submit **plasma** specimens with **original** C-384 form to:

Daniel F. Hayes, M.D.
Lombardi Cancer Center
Room E504
Research Building
3970 Reservoir Road, NW
Washington, DC 20007

and a copy of C-384 form to CALGB DMC; keep a copy for your records.

6.2.4 Submit **urine** specimens with **original** C-449 form to:

Daniel F. Hayes, M.D.
Lombardi Cancer Center
Room E504
Research Building
3970 Reservoir Road, NW
Washington, DC 20007

and a copy of C-449 form to CALGB DMC; keep a copy for your records.

6.2.5. Send Family History of Cancer Questionnaire to the CALGB DMC:

CALGB Data Management Center
2200 West Main Street, Suite 340
Durham, NC 27705

7.0 DATA SUBMISSION

FORM		Submission Schedule
C-350	CALGB Pathology Routing Form (for tissue blocks) Surgical path report	Submit both form and report regardless of whether or not block is sent. Submit with either tissue block from surgical specimen (breast or node) OR letter from pathologist stating reason for nonsubmission of block. Submit prior to first chemo/RT treatment.
C-383	CALGB Specimen Routing Form (for whole blood)	Submit with whole blood specimens. Submit prior to first chemo/RT treatment.
C-384	CALGB Specimen Routing Form (for plasma)	Submit with plasma specimen. Submit prior to first chemo/RT.
C-449	CALGB Specimen Routing Form (for urine)	Submit with urine specimen. Submit prior to first chemo/RT. For adjuvant studies using chemotherapy, submit prior to treatment, at the completion of treatment, and at each follow-up visit scheduled in the treatment protocol. For adjuvant studies using hormone therapy, submit prior to treatment and at each follow-up visit scheduled in the treatment protocol. For metastatic studies using chemotherapy, submit prior to treatment, on day one of each cycle, and at each follow-up visit scheduled in treatment protocol. For metastatic studies using hormone therapy, submit prior to treatment and at each follow-up visit scheduled in the treatment protocol.
C-377	Family History of Cancer Questionnaire	Within 2 wks of registration onto CALGB 9484. If the patient declines to complete the questionnaire, it should be submitted with "PATIENT DECLINED" and the date written across the top.

8.0 METHODS

8.1 ***Patient entry:*** Eligible patients are entered on this protocol if they consent at the time they are enrolled on the treatment protocol and meet study eligibility requirements given in section 4.0.

8.2 ***FFPE tissue:*** A representative block of the primary tumor is best for biologic markers and histologic correlations, but both primary and nodal tissues are acceptable for biologic assays. If insufficient primary or nodal tissue is available for submission of one block, a brief explanatory note from the institutional pathologist within six months of patient entry will suffice.

Submission of representative tissue sections on glass slides is not acceptable since the tissues must be processed in different ways for various assays: 4μ on glass slides for HE staining and immunohistochemistry, 10μ for DNA extraction, and 30μ for nuclear isolation for flow cytometry. The CALGB Pathology Office at Roswell Park Cancer Institute will prepare these sections as there is some evidence that antigen loss may occur over time on cut sections unless maintained at a low temperature.

Each submitted block will be carefully protected and monitored by the CALGB Pathology Office so that depletion of the block is minimized and a minimum of three recut HE sections remain on file at all times. National Institutes of Health directives call for the indefinite retention of each submitted block for future, as yet undetermined, biologic/genetic assays. Upon request for any emergent clinical or legal reason, the remaining portion of the block and one HE section will be returned by overnight mail to the originating Institutional Pathology Laboratory .

Tissue blocks from the operative (not needle biopsy) specimen along with the corresponding surgical pathology report and original Form C-350, CALGB Tissue Routing Form must be submitted to:

Dr. Maurice Barcos, Chair
CALGB Pathology Office
Roswell Park Memorial Institute
Department of Pathology
Elm and Carlton Streets
Buffalo, NY 14263
716-845-4443

Institutional data managers will arrange for submission of tissue blocks to the above address by contacting the appropriate pathologist at a CALGB main member or affiliate institution.

Somatic DNA: From the specimens collected as described above, individual investigators will prepare DNA according to their established laboratory procedures. It is anticipated that somatic DNA will be derived from the tumor specimen, but somatic DNA abnormalities may also be sought in normal tissue adjacent to the tumor.

8.3 Timepoints for collection of plasma, urine, and whole blood for genomic studies:

8.3.1 For Adjuvant studies using chemotherapy:

Collect whole blood for plasma and urine samples from patients prior to treatment initiation, at the completion of therapy, and at each follow-up treatment visit scheduled in the treatment protocol.

Collect whole blood separately for genomic DNA studies prior to treatment initiation only for those patients who have signed the portion of the consent form for studies of heritable cancer genes.

8.3.2 For Adjuvant studies using hormone therapy:

Collect whole blood for plasma and urine samples from patients prior to treatment initiation and at each follow-up treatment visit scheduled in the treatment protocol.

Collect whole blood separately for genomic DNA studies prior to treatment initiation only for those patients who have signed the portion of the consent form for studies of heritable cancer genes.

8.3.3 For Metastatic Studies using chemotherapy:

Collect whole blood for plasma and urine samples from patients prior to treatment initiation, on day one of each cycle of treatment, and at each follow-up visit scheduled for the treatment protocol.

Collect whole blood separately for genomic DNA studies prior to treatment initiation only for those patients who have signed the portion of the consent form for studies of heritable cancer genes.

8.3.4 For Metastatic Studies using hormone therapy:

Collect whole blood for plasma and urine samples from patients prior to treatment initiation and at each follow-up visit scheduled for the treatment protocol.

Collect whole blood separately for genomic DNA studies prior to treatment initiation only for those patients who have signed the portion of the consent form for studies of heritable cancer genes.

8.4 Collection and handling instructions for plasma, urine, and whole blood for genomic studies

8.4.1 Plasma collection and handling:

Collect 10cc of whole blood by venipuncture into an EDTA-containing (purple top) collection tube.

Centrifuge blood at 3000Xg for ten minutes (standard clinical centrifuge). Then aliquot supernatant plasma into a separate tube and label the tube with the patient's name, CALGB number, hospital number, the date of collection, the participating institution, and the number of the CALGB clinical protocol to which the patient is registered.

Separation (centrifuging, aliquoting) the plasma should be performed within 4-6 hours of collection. Samples may be stored at 4°C (regular ice, or regular refrigerator) for not more than 24 hours prior to storage at -20°C (a standard refrigerator freezer).

Both plasma and urine samples can be stored at -20°C at participating institution until several have accumulated. These samples can be mailed as batches (10-20 specimens or more) on dry ice overnight to the Lombardi Cancer Center at the address below. An original C-384 form must be submitted with each sample, with a copy of the form sent to the DMC.

Be certain that at least five (5) pounds of dry ice are used. Also, ship overnight express so that specimens will not arrive on a weekend or holiday. Address:

Daniel F. Hayes, M.D.
Lombardi Cancer Center
Room E504
Research Building
3970 Reservoir Road, NW
Washington, DC 20007
Telephone: 202-687-2103

8.4.2 Urine collection and handling:

Collect 50 ml (or more) clean catch urine into sterile urine collection container.

Centrifuge urine at 200g for 3 minutes (standard clinical centrifuge).

Pour spun urine into plastic freezing tube and label with the patient's name, CALGB number, hospital number, the date of collection, the participating institution, and the number of the CALGB clinical protocol to which the patient is registered.

Separation (centrifuging, aliquoting) the urine should be performed within 4-6 hours of collection. Samples may be stored at 4°C (regular ice, or regular refrigerator) for not more than 24 hours prior to storage at -20°C (a standard refrigerator freezer).

Both plasma and urine samples can be stored at -20°C at participating institution until several have accumulated. These samples can be mailed as batches (10-20 specimens or more) on dry ice overnight to the Lombardi Cancer Center at the address below. An original C-449 form must be submitted with each sample, with a copy of the form sent to the DMC.

Be certain that at least five (5) pounds of dry ice are used. Also, ship overnight express so that specimens will not arrive on a weekend or holiday. Address:

Daniel F. Hayes, M.D.
Lombardi Cancer Center
Room E504
Research Building
3970 Reservoir Road, NW
Washington, DC 20007
Telephone: 202-687-2103

8.4.3 Collection of whole blood for Genomic DNA studies:

Genomic DNA: Note: A separate portion of the consent form used for treatment studies must be signed for studies of genomic DNA.

One to two 8cc tubes of whole blood should be drawn in yellow topped tubes (Vacutainer #4606; acid-citrate dextrose solution). Two tubes are preferable. Collect and store tubes at ambient temperature (70°F, 25°C). Blood should **NOT** be refrigerated but should be stored in a cool place. Blood should be shippted within 24 hours of collection, at ambient temperature. Cold packs are not required. An original C-383 form must be submitted with each sample, with a copy of the form sent to the DMC. Ship to:

Qing Yang/Daynice Skeen/Lynn Dressler
UNC DNA Extraction Laboratory
University of North Carolina
CB #7295 Lineberger Cancer Research Center
Mason Farm Road, Room 350
Chapel Hill, NC 27599-7295

Note: Blood samples should be sent by overnight carrier, Monday through Thursday. (For Thursday shipment, please send by priority overnight.) **DO NOT SHIP BLOOD ON FRIDAYS OR THE DAY BEFORE A HOLIDAY.**

If it is absolutely necessary to draw blood on a Friday or the day before a holiday, keep the blood at ambient temperature. Blood should be shipped within 72 hours. Therefore, blood drawn on a Friday should be shipped on Monday by overnight carrier for Tuesday delivery.

The UNC DNA Extraction Laboratory will perform leukocyte separation and DNA extraction. Lymphocyte DNA will be prepared using the ABI DNA extractor and the DNA stored at -70°C. The methods to be employed are those already in place for studies of ras mutations in leukemic cells by the CALGB.

8.5 **Shipment billing:** A Federal Express account has been established for this study. This account number should be used exclusively for shipment of specimens as detailed above. The Federal Express account number may be obtained by contacting the Protocol Assistant at the CALGB Central Office: 773-702-9171.

8.6 **Self-Administered Family History of Cancer Questionnaire:** After the patient gives informed consent and is registered to CALGB 9484, the patient will be given a self administered questionnaire covering the above topic. The questionnaire requires a short time to complete and should be submitted within 2 weeks of entry onto CALGB 9484. The institutional data managers should use the self-addressed envelope to send the completed questionnaires to:

CALGB Data Management Center
2200 West Main Street, Suite 430
Durham, NC 27705
Phone: 919-286-0045
Fax: 919-286-1142

The CALGB DMC will forward a copy of the questionnaires to the Specialized Registry staff at the Epidemiology Office of the University of North Carolina.

A sub-sample of patients identified on the basis of information provided by the self-administered questionnaire (CALGB Family History of Cancer Questionnaire) will be contacted by the epidemiology office staff at the University of North Carolina, Chapel Hill, and asked to complete a more extensive phone interview (CALGB Detailed Family History and Exposure Telephone Interview). The participating epidemiology staff is funded by a grant, so the phone interviews will be conducted at no charge to patients or their families. Prior to contacting patients by phone, the epidemiology staff will contact the institution that registered the patient to assure that the patient is still alive and not hospitalized, in order to minimize stress to the patient and/or family.

8.7 **Receipt of Specimens:** A system is being implemented so that Centers receiving specimens will electronically report to the CALGB database the receipt and condition of the specimen using standard CALGB procedures. However, until this system is fully operational, initiating Centers will e-mail or fax this information to the responsible data coordinator at the Data Management Center.

8.8 Tracking of Patient Specimen Submission: The CALGB data management system (or data coordinator, until the system is fully implemented) will track patients who are entered on this CALGB protocol and generate reminders to institutions that have entered patients on this protocol if the specimens are not received at the appropriate office or lab in a timely manner.

8.9 Training of data managers: On a regular basis, not less than once a year, a portion of the CALGB Clinical Research Associates workshop will be devoted to instruction of the proper methods of obtaining and shipping the above specimens.

8.10 Specialized Registry Policies: Application for use of Registry. Use of the registry is under the supervision of the Specialized Registry Steering Committee appointed by Dr. O. Ross McIntyre, M.D. the Principal Investigator on the grant from the U.S. Army Medical Research and Materiel Command which supports the registry. Charter members of the Steering Committee are listed below:

Name	CALGB position	Institution
O. Ross McIntyre, M.D.	Chairman.	Dartmouth Medical School
Robert Millikan, DVM, Ph.D	Co-PI	U. North Carolina
Maurice Barcos, M.D.	Pathology	Roswell Park
Donald Berry, Ph.D.	Statistician	Duke Univ.
Larry Norton, M.D.	Br. Com. Chm	Memorial Sloan-Kettering
Lauren Schnaper, M.D.	Surgery	U. Maryland
Edison Liu, M.D.	Chm. Cor. Sci.	U. North Carolina
Dale Sandler, Ph.D.	Chm. Epi. Com	NIEHS
Daniel Hayes, M.D.	Vice Chm. Br. Com.	Dana Farber
Judy Garber, M.D.	Member, Cor Sci	Dana Farber
Alice Kornblith, Ph.D.	Member, Psy Onc	Memorial Sloan-Kettering
Deborah Collyar	Patient Advocate	
Sue Moore	Patient Advocate	

Additional members may be appointed to the steering committee from time to time and will be noted in revisions to this protocol. However, it is anticipated that there will be minimal turnover of steering committee membership.

Laboratory and epidemiological studies that are approved by the Steering Committee for the use of the Specialized Registry will be kept on file at the CALGB Central Office and incorporated into this appendix. Each project will have received IRB approval at the submitting investigator's institution. Individual projects will not require IRB approval at individual CALGB institutions.

Procedures for Project Approval/Appendix Inclusion: Investigators wishing to use the resources of the registry must apply to the Steering Committee for permission to obtain materials or information from the registry. In each case the investigator must submit a protocol for the proposed study and furnish evidence that it has been reviewed and approved by the Institutional Review Board at the investigator's institution. In addition, the investigator must accept other conditions governing the collaboration. If the investigator is a member of CALGB, usual policies governing Group data management and publication will prevail. If the user is not a member of CALGB, a CALGB co-chair of the proposed study will be appointed by the Steering Committee in consultation with the investigator. The person serving as co-chair will assist in trouble-shooting and will present a synopsis of the status of the study at CALGB meetings, if the non-CALGB investigator is unable to attend. The investigator will be asked to sign a letter outlining the essential features of the collaboration with the Specialized Registry. An important feature of the collaboration is that the investigator will furnish results to the CALGB Data Management Center where analyses will be performed by the CALGB statistician. No information concerning the patient, other than the specimen from an individual on a CALGB trial, will be furnished to the investigator. In this manner the laboratory will remain blinded as to

the other information available about the patient and patient confidentiality will be protected as well. The letter stipulates that the investigator will not provide specimens received from the registry to third parties. These procedures have been put in place in order to: protect patient confidentiality; blind the laboratory doing tests with respect to patient outcomes until the laboratory has submitted its results and the responsible CALGB statistician has performed an analysis; and achieve agreement on the presentation and publication of results prior to commencing with the work.

It is anticipated that the Specialized Registry will be used by a large number of investigators. This protocol will not be amended to describe the details of each laboratory or other use to which an approved investigator may put the Registry, however, as stated above each project using the Registry will have received IRB approval at the investigator's institution. It is anticipated that methodologies in the laboratories will be rapidly evolving during the lifetime of the Registry and that a number of hypotheses will be offered in the future that could not be conceived today. The patients have been given assurance that the Registry will approve studies that are limited to those involving cancer, and it is not intended to reconsent the patient for each new test for which the registry will be used.

Studies of heritable cancer genes will be conducted according to CALGB policies for the studies of such genes.

9.0 REFERENCES

1. Rothman K. Modern Epidemiology, pp 95-96, Little Brown, Boston, 1986.

2. Khoury M, James L. Population and familial relative risks of disease associated with environmental factors in the presence of gene-environment interactions. Am. J Epidemiol. 137:1241-50, 1993.

3. Charrow RP. Bench Notes- Judgements: Whose Tissue is it, Anyway? Jr. NIH Research, 6: 79-81, 1994

4. Kaaks R, Tweel I, van Noord P, Riboli E. Efficient use of biological banks for biochemical epidemiology: exploratory hypothesis testing by means of a sequential t-test. Epidemiology 5: 429-38, 1994.

5. Begg C, Zhang Z. Statistical analysis of molecular epidemiology studies employing case-series. Cancer Epidemiology Biomarkers & Prevention 3: 173-75, 1994.

10.0 MODEL CONSENT CALGB 9484: LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

About Using Specimens and Interviews for Research

We would like to keep some of the left over tissue from your biopsy or surgery for future research. If you agree, this tissue will be sent to a repository where it will be preserved. Pieces of the tissue will be used in research to learn more about cancer. Precautions will be taken not to use up all of the cancer tissue in the specimen. If your institution ever needs the tissue again, the repository will return it in good condition within 24 hours.

The CALGB would also like to obtain some blood samples and urine samples from you. The blood sample will allow researchers to examine genes in cells that are not cancerous, and to look for substances in the plasma that may result from or contribute to the development of breast cancer. The urine samples may also be useful for similar purposes.

Because it is not possible for you or the CALGB to know what will be discovered in the future and what additional tests may be appropriate at that time, we ask that you give permission for such studies without being recontacted for permission for each test. The research that may be done with your tissue and blood or urine samples probably will not help you. It might help people who have cancer and other diseases in the future.

CALGB may also wish to contact you by phone in order to ask questions about things that may relate to the cause and prevention of breast cancer.

If you agree, we will use your blood cells for genetic research (about diseases that are passed on in families). If your specimens are used for this kind of research, the results will not be returned to your hospital or doctor or put in your health records. If you do not want your blood cells to be used for genetic research, you can still agree to have your tissue and urine used for other types of research that do not involve diseases that are passed on in families.

The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over tissue or to furnish the blood and urine specimens for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that we can have the specimens and you decide to change your mind later, just contact us and let us know that you do not want us to use your specimens. Then they will no longer be used for research.

When tests have been completed with the specimens you have decided to let us have, the results may be combined with other information about you. Test results and information about you and your treatment are maintained in a confidential file in the CALGB computer. Only the responsible person at the CALGB database is able to combine the results of tests on your tissue, blood or urine with other information about you, for instance, how well you respond to treatment. We will not reveal your name or other identifying information about you and your illness to researchers who perform the testing or anyone else. The CALGB has obtained a Certificate of Confidentiality from the U.S. Department of Health and Human Services that will also help to protect this information.

Your tissue will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future.

Benefits

The benefits of research using the specimens include learning more about what causes cancer, and how to prevent, treat, and cure it.

Risks

There are very few risks to you. The risk of giving the blood sample when blood is being collected for tests required to manage your care is minimal as is the collection of the urine sample. The greatest risk is the release of information about you. The CALGB will protect your records so that your name, address, and phone number will be kept private. The chance that this information will be discovered by someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No." No matter what you decide to do, it will not affect your care. If you have any questions, please talk to your doctor or nurse, or call the Institutional Review Board (IRB) representative (phone number given below).

1. My tissue may be kept for use in research to learn about, prevent, treat, or cure cancer.

   Yes No

---

2. An interviewer from CALGB may contact me by phone to ask questions that relate to the cause, prevention and treatment of breast cancer.

   Yes No

---

3. I also give my permission to be contacted by phone in the future if it might assist in this kind of research.

   Yes No

---

4. I give permission for blood samples to be obtained that will be used for tests of cancer genes that may run in families. I understand that the results of this type of test will remain confidential in the CALGB computer file and will not be returned to me, my hospital or my doctor.

   Yes No

---

5. I give my permission for urine and plasma (blood) samples to be obtained for tests relating to cancer.

   Yes No

(Patient's Signature)	(Date)
(Physician's Signature)	(Date)
(Name of Responsible Investigator)	(Phone #)
(Name of IRB Representative)	(Phone #)

APPENDIX I

Data Collection Forms

C-350 CALGB Pathology Routing Form

C-383 CALGB Specimen Routing Form: Whole Blood

C-384 CALGB Specimen Routing Form: Plasma

INSTRUCTIONS FOR
CALGB: TRACKING FORM (TISSUE BLOCKS)
NO. C-490

A. PURPOSE

To track sample submission and receipt of information for tissue blocks submitted as part of the protocol.

B. FORM SPECIFIC INSTRUCTIONS

1. If the data on this form are amendments to previously submitted data, indicate this by checking "YES" in the box in the upper right corner of the form; otherwise leave this space blank. Highlight and circle all amended data.

2. Record patient's name, hospital number and main member institution/adjunct information for all patients. Only complete the participating group information if you are a member of a group other than CALGB.

3. When completing "specify" fields try to limit comment wording to 20 or fewer characters for computer data entry. A more complete explanation may be provided underneath the field or with an addendum.

4. The SUBMITTING INSTITUTION must indicate if the sample has been sent along with the form. Complete the information in the box on the LEFT as indicated. Note that date sample collected refers to the date the tissue was removed from the patient. Path number is the pathology identification number or accession number used by the institution to identify this sample. Specify the date blocks were sent and the sender's name and phone number. The submitting institution should retain a copy of the form and submit a copy to the CALGB Data Management Center. The original should be included with the blocks.

5. NOTE: ALL BLOCKS SUBMITTED MUST BE ACCOMPANIED BY THIS FORM AND APPROPRIATE PATHOLOGY REPORT(S). See the Sample Submission section of the protocol for details.

6. The RECEIVING INSTITUTION must complete the information in the box on the RIGHT as indicated. Specify the date blocks were received and the receiver's name and phone number. A copy of this from should be kept for his/her records and the original should be sent to the CALGB Data Management Center, 2200 West Main Street, and Suite 340, Durham, North Carolina 27705.

CALGB: TRACKING FORM (TISSUE BLOCKS)

CALGB Form:	C-490
CALGB Study No.:	_____
CALGB Patient ID:	_____
Amended Data?:	___ Yes

INSTRUCTIONS: This form is to be completed and submitted as required by protocol. Information in the upper right box must be completed for this form to be accepted. Do not leave any entries black. Enter -1 to indicate that an answer is unknown, unobtainable, not applicable, or not done. Retain a copy for your records and submit a copy to Data Management Center. Submit original with required samples and appropriate report(s) to the pathology coordinating office mentioned in the histology specimen submission section of your protocol.

Patient's Name _____ Participating Group _____

Patient Hospital number _____ Participating Group Protocol No. _____

Main Member Institution/Adjunct _____ Participating Group Patient No. _____

☐ **Does specimen accompany this form? (1-No, 2-Yes)**
If no, specify reason: _____

If yes, complete the remainder of this form.

☐ **Is this patient enrolled in a companion study? (1-No, 2-Yes)** ☐☐☐☐ **If yes, please give companion study number.**

TO BE COMPLETED BY SUBMITTING INSTITUTION

☐☐ ☐☐ ☐☐☐☐ Date Sample Collected
M D Y

☐☐ Sample extraction
(01-Biopsy, 18-Lumpectomy, 06-Mastectomy)

☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ Pathology/accession no.:

☐☐ ☐☐ ☐☐☐☐
M D Y
Date blocks and pathology reports submitted

_____
Submitted By

_____
Phone No.

TO BE COMPLETED BY RECEIVING INSTITUTION

☐☐ ☐☐ ☐☐☐☐ Date Sample Received
M D Y

☐☐ Sample condition
1- ok 3-missing
2-damaged 11-poor fixation

☐ Pathology report received? (1-No, 2-Yes)

☐ Does block match path report? (1-No, 2-Yes)

_____
Received By

_____
Phone No.

INSTRUCTIONS FOR CALGB SPECIMEN ROUTING FORM (C-383): WHOLE BLOOD

A. Purpose: To provide identifying information that will accompany the tube(s) of whole blood.

B. Form Specific Instructions:

1. If any data on this form is an amendment to previously submitted data, indicate this by checking "Yes" in the box located in the upper right-hand corner of the form; otherwise, leave this space blank. Highlight and circle ALL amended data.

2. Record the patient's name, hospital number and main member institution/adjunct information. Only complete the participating group information if you are a member of a group other than CALGB (EGOC, SWOG, etc.).

3. Record the CALGB study number (the correlative science study number) in the box located in the upper right-hand corner of the form. Record the CALGB treatment study number in the section entitled "To be completed by submitting institution".

4. The SUBMITTING INSTITUTION must complete the information in the TOP PORTION of the form, as indicated. Do NOT add decimal points or boxes to any data on this form.

5. Record the month, day, and 4-digit year that the tube(s) of whole blood were collected from the patient.

6. Code whether the specimen will accompany this form to the sample collection site. If the specimen does NOT accompany this form, be sure to specify the reason.

7. Record the number of tubes of whole blood being submitted.

8. Record the month, day, and 4-digit year that the tube(s) of whole blood were sent.

9. Code whether the specimen collected is a pre-treatment sample, was collected during initial treatment, during follow-up (the patient is no longer receiving the protocol treatment) or at the time of relapse. Ship each specimen separately (e.g. pre-treatment specimen versus during treatment specimen versus follow-up specimen, etc.).

10. Upon completion of the top portion of the form, print or type your name and the date you completed the form. Make two copies of this form, keep one copy for your records and send the other copy to the CALGB Data Management Center. Submit the original form along with the sample to the appropriate CALGB laboratory, as specified by the protocol.

11. See the Sample Submission section of the protocol for PACKAGING and SHIPPING instructions.

12. The RECEIVING INSTITUTION must complete the MIDDLE PORTION of the form as indicated. Specify the date the sample was received and the name of the receiver. If the exact volume of aliquot is unknown, estimate the average volume. Return a copy of the entire form to the CALGB Data Management Center.

13. The section FOR DMC USE ONLY has been pre-coded. Do not edit this portion.

CALGB: SPECIMEN ROUTING FORM:
WHOLE BLOOD

CALGB Form:	C-383
CALGB Study No.:	_____
CALGB Patient ID.:	_____
Amended Data?:	_____ Yes

INSTRUCTIONS: The original of this form is to be completed and submitted along with required whole blood specimen. Information in the upper right box must be completed for this form to be accepted. Do not leave any entries blank. Circle and highlight all amended data. Enter -1 to indicate that an answer is unknown, unobtainable, not applicable, or not done. Retain a copy of this form for your records and submit a copy to the CALGB Data Management Center. Submit the original form with the specimen to the appropriate CALGB Laboratory. SEE THE PROTOCOL FOR PACKAGING AND SHIPPING INSTRUCTIONS.

Patient's Name _____ Participating Group _____

Patient Hospital Number _____ Participating Group Protocol No. _____

Main Member Institution/Adjunct _____ Participating Group Patient No. _____

TO BE COMPLETED BY SUBMITTING INSTITUTION

[1] Blood Sample **(whole blood)** [ ][ ] [ ][ ] [ ][ ][ ][ ] Date whole blood specimen collected (M D Y)

[ ][ ][ ][ ][ ][ ] CALGB Treatment Study [ ] Does specimen accompany this form? (1-No, 2-Yes)

If ***no***, specify reason: _____

If ***yes***, complete the remainder of this form.

[ ][ ] Number of tubes submitted [ ][ ] [ ][ ] [ ][ ][ ][ ] Date sample sent (M D Y)

[ ][ ] Specimen Collected

02-Pre-treatment
21-During Initial Treatment
18-During Follow-up, No Therapy
14-At Relapse/Progression

Responsible treating physician: _____

Completed By: _____ **Date Completed:** ____/____/____
(Print or Type Name)

Phone Number to be used in event of sample problems: _____

TO BE COMPLETED BY RECEIVING INSTITUTION/LABORATORY

[ ][ ] Sample Condition [ ][ ] [ ][ ] [ ][ ][ ][ ] Date sample received (M D Y)

01-Okay
02-Damaged
03-Missing
07-Insufficient amount
16-Damaged but stored
17-Thawed but stored
19-Improperly stored

[ ][ ][ ][ ][ ][ ][ ][ ][ ] Sample ID no. [ ][ ] # of Aliquots [ ][ ][ ] Average aliquot volume (cc)

Sample received by _____

FOR DMC USE ONLY

[1] Specimen Type (1: peripheral blood)
[1] Blood Sample (1: whole blood)
[8] Method of Sample Collection (8: venous)
[6] Sample Container (6: yellow top vial)
[2] Class of Units (2: volume)
[1 5] Unit of Measure (15: cubic centimeter)
[1] Sample Storage (1: room temperature)

INSTRUCTIONS FOR
CALGB SPECIMEN ROUTING FORM (C-384):
PLASMA

A. Purpose: To provide identifying information that will accompany the tube(s) of plasma.

B. Form Specific Instructions:

1. If any data on this form is an amendment to previously submitted data, indicate this by checking "Yes" in the box located in the upper right-hand corner of the form; otherwise, leave this space blank. Highlight and circle ALL amended data.

2. Record the patient's name, hospital number and main member institution/adjunct information. Only complete the participating group information if you are a member of a group other than CALGB (EGOC, SWOG, etc.).

3. Record the CALGB study number (the correlative science study number) in the box located in the upper right-hand corner of the form. Record the CALGB treatment study number in the section entitled "To be completed by submitting institution".

4. The SUBMITTING INSTITUTION must complete the information in the TOP PORTION of the form, as indicated. Do NOT add decimal points or boxes to any data on this form.

5. Record the month, day, and 4-digit year that the tube(s) of plasma were **collected** from the patient.

6. Code whether the specimen will accompany this form to the sample collection site. If the specimen does NOT accompany this form, be sure to specify the reason.

7. Record the number of tubes of plasma being submitted.

8. Record the month, day, and 4-digit year that the tube(s) of plasma were **sent**.

9. Code whether the specimen collected is a pre-treatment sample, was collected during initial treatment, during follow-up (the patient is no longer receiving the protocol treatment) or at the time of relapse. Ship each specimen separately (e.g. pre-treatment specimen versus during treatment specimen versus follow-up specimen, etc.).

10. Upon completion of the top portion of the form, print or type your name and the date you completed the form. Make two copies of this form, keep one copy for your records and send the other copy to the CALGB Data Management Center. Submit the original form along with the sample to the appropriate CALGB laboratory, as specified by the protocol.

11. See the Sample Submission section of the protocol for PACKAGING and SHIPPING instructions.

12. The RECEIVING INSTITUTION must complete the MIDDLE PORTION of the form as indicated. Specify the date the sample was received and the name of the receiver. If the exact volume of aliquot is unknown, estimate the average volume. Return a copy of the entire form to the CALGB Data Management Center.

13. The section FOR DMC USE ONLY has been pre-coded. Do not edit this portion.

CALGB: SPECIMEN ROUTING FORM
PLASMA

CALGB Form:	C-384
CALGB Study No.:	_____
CALGB Patient ID.:	_____
Amended Data?:	_____ Yes

INSTRUCTIONS: The original of this form is to be completed and submitted along with required plasma specimen. Information in the upper right box must be completed for this form to be accepted. Do not leave any entries blank. Circle and highlight all amended data. Enter -1 to indicate that an answer is unknown, unobtainable, not applicable, or not done. Retain a copy of this form for your records and submit a copy to the CALGB Data Management Center. Submit the original form with the specimen to the appropriate CALGB laboratory. SEE THE PROTOCOL FOR PACKAGING AND SHIPPING INSTRUCTIONS.

Patient's Name _____ Participating Group _____

Patient Hospital Number _____ Participating Group Protocol No. _____

Main Member Institution/Adjunct _____ Participating Group Patient No. _____

TO BE COMPLETED BY SUBMITTING INSTITUTION

[4] Blood Sample **(plasma)**

[ ][ ] [ ][ ] [ ][ ][ ][ ] Date plasma specimen collected
M D Y

[ ][ ][ ][ ][ ][ ] CALGB Treatment Study

[ ] Does specimen accompany this form? (1-No, 2-Yes)

If ***no***, specify reason: _____

If ***yes***, complete the remainder of this form.

[ ][ ] Number of tubes submitted

[ ][ ] [ ][ ] [ ][ ][ ][ ] Date sample sent
M D Y

[ ][ ] Specimen Collected
02-Pre-treatment
21-During Initial Treatment
18-During Follow-up, No Therapy
14-At Relapse/Progression

Responsible treating physician: _____

Completed By: _____ **Date Completed:** ____/____/____
(Print or Type Name)

Phone Number to be used in event of sample problems: _____

TO BE COMPLETED BY RECEIVING INSTITUTION/LABORATORY

[ ][ ] Sample Condition
01-Okay
02-Damaged
03-Missing
07-Insufficient amount
16-Damaged but stored
17-Thawed but stored
19-Improperly stored

[ ][ ] [ ][ ] [ ][ ][ ][ ] Date sample received
M D Y

[ ][ ][ ][ ][ ][ ][ ][ ][ ] Sample ID no.

[ ][ ] # of Aliquots

[ ][ ][ ] Average aliquot volume (cc)

Sample received by _____

FOR DMC USE ONLY

[1] Specimen Type (1: peripheral blood)
[4] Blood Sample (4: plasma)
[8] Method of Sample Collection (8: venous)
[4] Sample Container (4: purple top vial)

[2] Class of Units (2: volume)
[1][5] Unit of Measure (15: cubic centimeter)
[7] Sample Storage (7: -20 degrees C)

INSTRUCTIONS FOR
CALGB URINE SAMPLE TRACKING FORM
NO. C-449

A. Purpose

To track sample submission and receipt information for urine samples submitted as part of the protocol. This form is to be submitted as required by protocol.

B. Form Specific Instructions

1. If any data on this form is an amendment to previously submitted data, indicate this by checking "Yes" in the box located in the upper right-hand corner of the form; otherwise, leave this space blank. Highlight and circle ALL amended data.

2. Record the patient's name, hospital number and main member institution/adjunct information. Only complete the participating group information if you are a member of a group other than CALGB (ECOG, SWOG, etc.).

3. Record the CALGB study number (the correlative science study number) in the box located in the upper right-hand corner of the form. Record the CALGB treatment study number in the section entitled "To be completed by submitting institution".

4. The SUMBITTING INSTITUTION must complete the information in the TOP PORTION of the form, as indicated. Note that the "date sample collected" refers to the date the sample was collected from the patient. Also specify the date the sample was sent and the responsible treating physician's name. Time should be recorded using military clock (i.e., a 24-hour clock). If the exact time of sample collection is unknown, fill in a reasonable estimate of time. If the exact volume of the sample is unknown, an estimated volume is acceptable. Do NOT add decimal points or boxes to any data on this form.

5. Upon completion of the top portion of the form, print or type **your name** and the date you completed the form. Make two copies of this form, keep one copy for your records and send the other copy to the CALGB Data Management Center. Submit the original form along with the sample to the appropriate CALGB laboratory, as specified by the protocol.

6. See the Sample Submission section of the protocol for PACKAGING and SHIPPING instructions.

7. The RECEIVING INSTITUTION must complete the MIDDLE PORTION of the form as indicated. Specify the date the sample was received and the name of the receiver. If the exact volume of aliquot is unknown, estimate the average volume. Return a copy of the entire form to the CALGB Data Management Center.

8. The section FOR DMC USE ONLY has been pre-coded. Do not edit this portion.

CALGB: URINE SAMPLE TRACKING FORM

INSTRUCTIONS: This form is to be completed and submitted as required by protocol. Information in the upper right box must be completed for this form to be accepted. Do not leave any entries blank. Enter -1 to indicate that an answer is unknown, unobtainable, not applicable, or not done. Retain a copy of this form for your records and submit a copy to the CALGB Data Management Center. Submit the original form with the sample to the appropriate CALGB laboratory. SEE THE PROTOCOL FOR PACKAGING AND SHIPPING INSTRUCTIONS.

CALGB Form: C-449
CALGB Study No.: _____
CALGB Patient ID.: _____
Amended Data?: _____ Yes

Patient's Name _____ Participating Group _____

Patient Hospital Number _____ Participating Group Protocol No. _____

Main Member Institution/Adjunct _____ Participating Group Patient No. _____

TO BE COMPLETED BY SUBMITTING INSTITUTION

☐☐ ☐☐ ☐☐☐☐ Date sample collected
M D Y

☐☐ Specimen Collected
02-Pre-treatment
21-During Initial Treatment
18-During Follow-up, No Therapy
14-At Relapse/Progression

☐☐☐☐☐☐ CALGB Treatment Study

☐☐ : ☐☐ Time sample collected (h:m 24 hour clock)

☐☐☐ Approximate Volume of sample (ml)

☐☐ ☐☐ ☐☐☐☐ Date sample sent
M D Y

NOTE: ALL URINE SAMPLES SHOULD BE STORED AND SHIPPED AT A TEMPERATURE OF -20 DEGREES CELSIUS.

Responsible treating physician: _____

Completed By: _____ **Date Completed:** ____/____/____
(Print or Type Name)

Phone Number to be used in event of sample problems: _____

TO BE COMPLETED BY RECEIVING INSTITUTION/LABORATORY

☐☐ Sample Condition
1-O.K.
2-Damaged
3-Missing
7-Insufficient amount
16-Damaged but stored
17-Thawed but stored
19-Improperly stored

☐☐ ☐☐ ☐☐☐☐ Date sample received
M D Y

☐☐☐☐☐☐☐☐☐ Sample ID no. ☐☐ # of Aliquots ☐☐☐ Average aliquot volume (ml)

Received by _____

FOR DMC USE ONLY

1 1 Specimen Type (11: urine)
1 4 Method of Sample Collection (14: urination)
2 0 Sample Container (20: plastic freezing tube)
2 Class of Units (2: volume)
1 2 Unit of Measure (12: millimeter)
7 Sample Storage (7: -20 degrees C)

APPENDIX II

Questionnaires

C-377 CALGB Family History of Cancer Questionnaire

CALGB Detailed Family History and Exposure Telephone Interview

FAMILY HISTORY OF CANCER QUESTIONNAIRE
INSTRUCTIONS FOR CALGB PERSONNEL

A. Purpose - The enclosed survey is part of a recently funded project entitled, "Linkage of Molecular and Epidemiologic Breast Cancer Investigations: A Specialized Registry."

We will be using family history information to select patients for participation in a Registry. The Registry will undertake a systematic collection of tumor specimens, as well as treatment outcome, epidemiologic, and molecular data from breast cancer patients enrolled in clinical trials sponsored by CALGB. Several research hypotheses will be investigated using the Registry, including the role of family history in breast cancer prognosis.

B. Form Specific Instructions

1. Please provide this survey to all patients participating in Protocols _____.

2. We request that the patient complete this questionnaire at the time of treatment with a *RED FELT TIP PEN*.

3. After the questionnaire is complete, return it to the data management representative at your institution.

4. The questionnaires will then be mailed to the CALGB Data Management Center at the following address:

CALGB Data Management Center
2200 West Main Street, Suite 340
Durham, North Carolina 27705

5. Please try to ensure that all patients on the Protocol are given this questionnaire.

If the patient cannot complete the questionnaire at the time of treatment, they may take it home, but should bring the questionnaire with them at the next treatment.

FAMILY HISTORY OF CANCER QUESTIONNAIRE

Instructions for Patient

Thank you for taking time to complete this confidential questionnaire.

We will ask you about the occurrence of breast and other cancer in your relatives. All of the information you provide on this questionnaire will be held in the strictest of confidence. Neither your name nor any identifying information will appear in any report of the survey.

Based upon your answers to the family history questions, we may wish to contact you again for further information. There is a place on the questionnaire for you to tell us how to reach you in the future. With your help, we hope to learn more about the causes of breast cancer.

At the end of the questionnaire on pages 10 and 11 are comment pages. Use these pages if you need to more fully explain any of your answers. You will also find a space to describe special feelings or insights that you may have about the causes of breast cancer.

If you have any questions about our study or the questionnaire, please feel free to call us toll free at:

1-800-xxx-xxxx Monday - Friday 9 a.m. - 5 p.m.

If a representative is not immediately available, you may leave a message and we will return your call as soon as possible.

When you finish the questionnaire, place it in the envelope provided, and return it to the nurse when she returns to your room.

Thank you very much for your participation.

FAMILY HISTORY OF CANCER QUESTIONNAIRE

INSTRUCTIONS FOR COMPLETING THIS SURVEY

Please proceed with the remainder of the questionnaire. We will be asking questions which require you to provide information about history of cancer in your close relatives.

Make an "X" through the circle which represents your chosen responses with a *RED FELT TIP PEN.*

Example:

Please answer all questions to the best of your ability.

IMPORTANT:

We are asking you about the occurrence of cancer in your full-blood relatives.

We are not referring to step-children, step-siblings, or other half-relations.

If you are adopted and are not able to provide information on blood relatives, please skip to comment pages 10 and 11 at the end of the questionnaire.

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form.	C-377
CALGB Study No.	
CALGB Patient ID.:	

Patient's Name_____ Participating Group_____

Patient Hospital Number_____ Participating Group Protocol No._____

Main Member Institution/Adjunct_____ Participating Group Patient No._____

Today's Date

What is your main language: E-English, S-Spanish, O-Other:

(E) (S) (O)

Do you have a phone? N-No,Y-Yes

(N) (Y)

Can we contact you again? N-No,Y-Yes

(N) (Y)

Can we contact you by phone or mail? N-No,Y-Yes

(N) (Y)

Please give us the names, addresses, and phone numbers of two people who will know where you are at all times:

Name:_____

Address:_____

_____

Telephone Number: (___) _____

Name:_____

Address:_____

_____

Telephone Number: (___) _____

What is your present marital status? N- Never Married, M-Married, W-Widowed, S-Separated, D-Divorced

(N) (M) (W) (S) (D)

Are you adopted? Y-Yes, N-No, D-Don't know

(N) (Y) (D)

If "Yes," please read the following:

If you are adopted and you DO NOT KNOW about the cancer history of your blood relatives, please skip to comment pages 10 and 11 at the end of the questionnaire.

We are asking about history of cancer in your blood relatives.

Do you have any full sisters?

(N) (Y) If yes, please specify how many _____

Do you have any full brothers?

(N) (Y) If yes, please specify how many _____

Do you have any daughters?

(N) (Y) If yes, please specify how many _____

Do you have any sons?

(N) (Y) If yes, please specify how many _____

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form: C-377
CALGB Study No.: _____
CALGB Patient ID.: _____

Relative		Is Relative Alive, Dead or Unknown	Current Age or Age at Death						Has this Relative ever had a diagnosis of cancer? No, Yes, or Unknown	Types of Cancer (fill more than one circle if necessary)				If other specify type of cancer
			Under 20	20 - 39	40 - 49	50 - 59	60 - 69	70 or over		Breast	Ovarian	Colon	Other	
Example		(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(4)	*Stomach*
1	Mother	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
2	Father	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
3	Sister1	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
4	Sister2	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
5	Sister3	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
6	Sister4	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
7	Sister5	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
8	Sister6	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
9	Sister7	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
10	Sister8	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
11	Sister9	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
12	Sister10	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
13	Brother1	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
14	Brother2	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form: C-377
CALGB Study No.: _____
CALGB Patient ID.: _____

	Relative	Is Relative Alive, Dead or Unknown	Current Age or Age at Death						Has this Relative ever had a diagnosis of cancer? No, Yes, or Unknown	Types of Cancer (fill more than one circle if necessary)				If other specify type of cancer
			Under 20	20 - 39	40 -49	50 - 59	60 -69	70 or over		Breast	Ovarian	Colon	Other	
15	Brother3	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
16	Brother4	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
17	Brother5	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
18	Brother6	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
19	Brother7	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
20	Brother8	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
21	Brother9	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
22	Brother10	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
23	Daughter1	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
24	Daughter2	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
25	Daughter3	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
26	Daughter4	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
27	Daughter5	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
28	Daughter6	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
29	Daughter7	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form: C-3
CALGB Study No.: _____
CALGB Patient ID.: _____

	Relative	Is Relative Alive, Dead or Unknown	Current Age or Age at Death						Has this Relative ever had a diagnosis of cancer? No, Yes, or Unknown	Types of Cancer (fill more than one circle if necessary)				If other specify type of cancer
			Under 20	20 - 39	40 -49	50 - 59	60 -69	70 or over		Breast	Ovarian	Colon	Other	
30	Daughter8	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
31	Daughter9	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
32	Daughter10	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
33	Son1	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
34	Son2	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
35	Son3	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
36	Son4	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
37	Son5	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
38	Son6	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
39	Son7	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
40	Son8	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
41	Son9	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
42	Son10	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form:	C-37
CALGB Study No.:	
CALGB Patient ID.:	

EXTENDED FAMILY

Do you have any other relatives who have been diagnosed with cancer? N-No,Y-Yes

(N) (Y)

If yes please complete the table below:

Relative	Alive or Dead	Type of Cancer
Example: Grandmother	Alive	Ovarian

CALGB Form:	C-377
CALGB Study No.:	_____
CALGB Patient ID.:	_____

FAMILY HISTORY QUESTIONNAIRE
COMMENT PAGE

THANK YOU FOR COMPLETING THE FORMAL PART OF OUR QUESTIONNAIRE. BASED UPON YOUR ANSWERS TO THES QUESTIONS, WE MAY CONTACT YOU IN THE FUTURE. YOU MAY BE ASKED TO PARTICIPATE IN FUTURE STUDIES WHIC ARE AIMED AT INCREASING OUR UNDERSTANDING OF BREAST CANCER. YOUR CONTRIBUTIONS TO THE ON-GOING EFFOR TO UNDERSTAND AND PREVENT BREAST CANCER ARE INVALUABLE TO US.

Please feel free to provide explanations for your answers to any of the preceding questions.

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form:	C-377
CALGB Study No.:	_____
CALGB Patient ID.:	_____

COMMENT PAGE

Please use this page to write down any special feelings or insights that you may have about breast cancer. We are interested in what you think may have caused your breast cancer.

Interviewer ID: _____
Time Interview Began: _____ am/pm
Time Interview Ended: _____ am/pm
Date of Interview: _____
Outcome Code: _____
Reference Date: _____

CALGB DETAILED FAMILY HISTORY AND EPIDEMIOLOGY TELEPHONE INTERVIEW

Hello, my name is _____. May I please speak with (RESPONDENT)? I'm calling from THE LINEBERGER CANCER RESEARCH CENTER AT THE UNIVERSITY OF NORTH CAROLINA CHAPEL HILL. WE ARE CONDUCTING A STUDY ON BEHALF OF CANCER AND LEUKEMIA GROUP B (CALGB).

A. Recently, you indicated your willingness to participate in a study we are conducting of breast cancer patients.
As you recall, we are conducting phone interviews as part of this study. We would like to ask you some questions about your health history. These questions will take about one hour to answer.
Is this a convenient time for you?

(If NO, reschedule.)

If YES:

Thank you very much. Your answers to these questions will help us to understand more about breast cancer. For your future reference here is my name and address:
Name:_____
Lineberger Comprehensive Cancer Center, University of North Carolina
CB# 7500, Chapel Hill, NC 27599
Phone: 1-800-449-0147

B. Your cooperation in the survey is entirely voluntary, and all the information collected will be confidential. Neither your name nor any other identifying information will appear in any report of the survey.

C. The interview will take about 60 minutes. First, I would like to verify some of the previous information you have provided to us.

GO TO SECTION A.

A. VERIFICATION OF PREVIOUS INFORMATION

I. DEMOGRAPHIC INFORMATION

A1. What is your birthdate? _____mm _____dd _____yyyy

A2. What is the highest degree or year of school you have completed? (DO NOT READ CATEGORIES)

[ ] LESS THAN 8 YEARS
[ ] 8 THROUGH 11 YEARS
[ ] 12 YEARS OR COMPLETED HIGH SCHOOL
[ ] SOME COLLEGE
[ ] COLLEGE GRADUATE
[ ] MASTERS
[ ] DOCTOR OR LAWYER (PH.D., M.D., J.D.,D.V.M.)
[ ] OTHER (SPECIFY: _____)

A3. Would you describe yourself as white, black, Hispanic, Asian, or other? (IF OTHER, PROBE FOR ETHNIC GROUP OR RACE)

[ ] WHITE
[ ] BLACK
[ ] HISPANIC OR MEXICAN AMERICAN
[ ] ASIAN OR PACIFIC ISLANDER
[ ] NATIVE AMERICAN
[ ] ALASKAN NATIVE
[ ] OTHER (SPECIFY: _____)

A4. What is your present marital status?

☐ Single
☐ Married
☐ Separated
☐ Divorced
☐ Widowed

A5. IF EVER MARRIED: What is the highest degree or year of school that your husband or partner completed? (DO NOT READ CATEGORIES; IF MORE THAN ONE HUSBAND/PARTNER, ASK FOR MOST RECENT)

[ ] LESS THAN 8 YEARS
[ ] 8 THROUGH 11 YEARS
[ ] 12 YEARS OR COMPLETED HIGH SCHOOL
[ ] SOME COLLEGE
[ ] COLLEGE GRADUATE
[ ] MASTERS
[ ] DOCTOR OR LAWYER (Ph.D., M.D., J.D.,D.V.M.)
[ ] OTHER (SPECIFY: _____)

A6. In what kind of community do you currently live?

Location	Living now in:
Large city (pop.>100,000)	
Suburb of large city	
Town or city (pop.50,000-100,000)	
Town (pop.<10,000)	
Rural, non-farm (in the country, but not a farm)	
On a farm	

II. FAMILY HISTORY OF CANCER

Now, I would like to review the information that you previously provided to us on the Self-Aministered Family History of Cancer Questionnaire.

First I would like to verify that we are asking about your **FULL BLOOD** Relatives.

A7. **Are you adopted?**

☐ **YES, if yes do you know the health status of your full blood relatives?**
☐Yes, then continue with Family History section. ☐ No, skip to B section and continue questions.

☐ **NO,not adopted, continue with Family History section.**

A8. Now I will be asking about all your full blood relatives and how many you have.

HOW MANY?

RELATIVES	NUMBER
SONS	
DAUGHTERS	
BROTHERS	
SISTERS	
PATERNAL AUNTS	
PATERNAL UNCLES	
MATERNAL AUNTS	
MATERNAL UNCLES	

Now, I will be asking about all of your relatives who have been diagnosed with cancer and those that have not had cancer. **(Names are optional if given and are for identification during interview only.)**

MOTHER'S INFORMATION

A9. Is your mother still living?

[ ] Yes (Name_____)
[ ] No, skip to A11.

A10. How old is your mother? ☐☐☐ , **skip to A12.**

A11. How old was your mother when she died? ☐☐☐

A12. Did your mother ever have breast cancer or ovary cancer?

[ ] YES, BREAST CANCER, ONE BREAST
[ ] YES, BREAST CANCER, BOTH BREASTS
[ ] YES, OVARY CANCER
[ ] NO
[ ] DON'T KNOW OR REMEMBER

A13. How old was she when it was first diagnosed? ☐☐☐ (BREAST)
☐☐☐(OVARY)

A14. Did your mother ever have any other kind of cancer?
[ ] Yes
[ ] No, skip to A17

A15. What other kind of cancer(s) did she have?	A16. How old was she when it was diagnosed?
a. _____	a. ☐ ☐ ☐
b. _____	b. ☐ ☐ ☐

FATHER'S INFORMATION

A17. Is your father still living?
[ ] Yes
[ ] No, SKIP TO A19

A18. How old is your father? ☐☐☐ SKIP TO A20

A19. How old was your father when he died? ☐☐☐

A20. Did your father ever have cancer?
[ ] Yes
[ ] No, skip to A23

A21. What kind of cancer(s) did he have?	A22. How old was he when it was diagnosed?
a. _____	a. ☐ ☐ ☐
b. _____	b. ☐ ☐ ☐
c. _____	c. ☐ ☐ ☐
d. _____	d. ☐ ☐ ☐

Let's continue with your sisters and brothers, both living and deceased.

SISTER'S INFORMATION

A23. Altogether, how many FULL sisters have you had? ☐☐ (Number)
[ ] None, or adopted

Sister's Inform.	Oldest sister		2nd sister		3rd sister		4th sister		5th sister	
A. 24 Is your (?) sister still living	yes	no go to A26	yes	no go to A26	yes	no go to A26	yes	no go to A26	yes	no go to A26
A. 25 How old is she?	Age		Age		Age		Age		Age	
A. 26 How old was she when she died?	Age		Age		Age		Age		Age	
A. 27 Did she ever have Breast Cancer or Ovary Cancer?	[] Yes, one breast [] Yes,both breast [] Yes ovary [] No [] DON'T KNOW		[] Yes, one breast [] Yes,both breast [] Yes ovary [] No [] DON'T KNOW		[] Yes, one breast [] Yes,both breast [] Yes ovary [] No [] DON'T KNOW		[] Yes, one breast [] Yes,both breast [] Yes ovary [] No [] DON'T KNOW		[] Yes, one breast [] Yes,both breast [] Yes ovary [] No [] DON'T KNOW	
A28 How old was she when it was first diagnosed?	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar
A29 Did she ever have any other kind of cancer?	yes	no	yes	no	yes	no	yes	no	yes	no
A30 What kind of cancer did she have?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
A31 How old was she when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
A32 Was she a twin or triplet?	yes	no	yes	no	yes	no	yes	no	yes	no
A33 If yes, was she an identical or fraternal twin, triplet?	ident	frat.	ident	frat	ident	frat	ident	frat	ident	frat

BROTHER'S INFORMATION

A34. Altogether how many FULL brothers have you had? ☐☐

Brothers' Inform.	Oldest brother		2nd brother		3rd brother		4th brother		5th brother	
A. 35 Is your (?) brother still living	yes	no go to A37	yes	no go to A37	yes	no go to A37	yes	no go to A37	yes	no go to A37
A. 36 How old is he?	Age		Age		Age		Age		Age	
A. 37 How old was he when he died?	Age		Age		Age		Age		Age	
A. 38 Did he ever have Cancer?	[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW	
A39 What kind of cancer did he have? Types:	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Types:	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.
A40 How old was he when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Age	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.
A41 Was he a twin or triplet?	yes	no	yes	no	yes	no	yes	no	yes	no
A42 If yes, was he an identical or fraternal twin, triplet?	ident	frat.	ident	frat	ident	frat	ident	frat	ident	frat

TWIN INFORMATION

A43. Are you a twin?

[ ] Yes
[ ] No, skip to A4?

A44. Which brother or sister is your twin?

[ ] Brother #☐, skip to A46
[ ] Sister #_

A45. Are you identical twins?

[ ] Yes
[ ] No
[ ] Don't Know

MOTHER'S SIDE OF FAMILY

Now I have some questions about other relatives. I will begin with your mother's parents and her side of the family.

A46. First, was your mother adopted?

[ ] Yes, skip to A77
[ ] No
[ ] Don't Know

Mother's Mother (Maternal Grandmother)

A47. Is your mother's mother still living?

[ ] Yes
[ ] No, Skip to A49

A48. How old is your mother's mother? _____Skip to A50

A49. How old was your mother's mother when she died? ___

A50. Did your mother's mother ever have breast cancer or ovary cancer?

[ ] Yes, breast cancer, one breast
[ ] Yes, breast cancer, both breasts
[ ] Yes, ovary cancer
[ ] No
[ ] Don't Know

A51. How old was she when it was first diagnosed?

____ (Breast)
____ (Ovary)

A52. Did your mother's mother ever have any other kind of cancer?

[ ] Yes
[ ] No
[ ] Don't Know

A53. What kind of cancer(s) did she have?=======A54. How old was she when it was diagnosed?

a._____ a.____
b._____ b.____
c._____ c.____

Mother's Father (Maternal Grandfather)

A55. Is your mother's father still living? [ ] Yes
[ ] No

A56. How old is your mother's father? ____

A57. How old was your mother's father when he died? ____

A58. Did your mother's father ever have have cancer?

[ ] Yes
[ ] No
[ ] Don't Know

A59. What kind of cancer(s) did he have?==A60. How old was he when it was diagnosed?

a._____ a.____
b._____ b.____
c._____ c.____

Now I will ask you about your mother's brothers and sisters, both living and deceased.

Mother's Sisters (Maternal Aunts)

A61. Altogether, how many FULL sisters or did your mother have? ____ (Number)
[ ] None

Mother's Sisters.	Oldest sister		2nd sister		3rd sister		4th sister		5th sister	
A62 Is her (?) sister still living	yes	no go to A64	yes	no go to A64	yes	no go to A64	yes	no go to A64	yes	no go to A64
A63 How old is she?	Age		Age		Age		Age		Age	
A64 How old was she when she died?	Age		Age		Age		Age		Age	
A65 Did she ever have Breast Cancer or Ovary Cancer?	[] Yes, one breast [] Yes,both breast [] Yes ovary [] No [] DON'T KNOW		[] Yes, one breast [] Yes,both breast [] Yes ovary [] No [] DON'T KNOW		[] Yes, one breast [] Yes,both breast [] Yes ovary [] No [] DON'T KNOW		[] Yes, one breast [] Yes,both breast [] Yes ovary [] No [] DON'T KNOW		[] Yes, one breast [] Yes,both breast [] Yes ovary [] No [] DON'T KNOW	
A66 How old was she when it was first diagnosed?	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar
A67 Did she ever have any other kind of cancer?	yes	no	yes	no	yes	no	yes	no	yes	no
A68 What kind of cancer did she have?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
A69 How old was she when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.

Mother's Brothers (Maternal Uncles)

A70. All together how many full brothers did your mother have? _____(Number)
_____None

Mother's Brothers	Oldest brother		2nd brother		3rd brother		4th brother		5th brother	
A71 Is your (?) mother's brother still living	yes	no go to A73	yes	no go to A73	yes	no go to A73	yes	no go to A73	yes	no go to A73
A72 How old is he?	Age		Age		Age		Age		Age	
A73 How old was he when he died?	Age		Age		Age		Age		Age	
A74 Did he ever have Cancer?	[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW	
A75 What kind of cancer did he have? Types:	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Types:	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.
A76 How old was he when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Age	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.

Now I have some questions about your father's parents and his side of the family.

A77. First, was your father adopted?

[ ] Yes, skip to A108
[ ] No
[ ] Don't Know

Father's Mother (Paternal Grandmother)

A78. Is your father's mother still living?

[ ] Yes
[ ] No

A79. How old is your father's mother? ___

A80. How old was your father's mother when she died? ___

A81. Did your father's mother ever have breast cancer or ovary cancer?

[ ] Yes, breast cancer, one breast
[ ] Yes, breast cancer, both breasts
[ ] Yes, ovary cancer
[ ] No
[ ] Don't Know

A82. How old was she when it was first diagnosed?

____ (Breast)
____ (Ovary)

A83. Did your father's mother ever have any other kind of cancer?

[ ] Yes
[ ] No
[ ] Don't Know

A84. What kind of cancer(s) did she have?

a._____
b._____
c._____

A85. How old was she when it was diagnosed?

a.____
b.____
c.____

Father's Father (Paternal Grandfather)

A86. Is your father's father still living?

[ ] Yes
[ ] No

A87. How old is your father's father? ___

A88. How old was your father's father when he died? ___

A89. Did your father's father ever have have cancer?

[ ] Yes
[ ] No
[ ] Don't Know

A90. What kind of cancer(s) did he have?===A91. How old was he when it was diagnosed?

a.______________ a.____
b.______________ b.____
c.______________ c.____

Now I will ask you about your father's brothers and sisters, both living and deceased.

Father's Sisters (Paternal Aunts)

A92. Altogether, how many FULL sisters or did your father have? ____ (Number)
[ ] None

Father's Sisters.	Oldest sister		2nd sister		3rd sister		4th sister		5th sister	
A93 Is his (?) sister still living	yes	no go to A95	yes	no go to A95	yes	no go to A95	yes	no go to A95	yes	no go to A95
A94 How old is she?	Age		Age		Age		Age		Age	
A95 How old was she when she died?	Age		Age		Age		Age		Age	
A96 Did she ever have Breast Cancer or Ovary Cancer?	[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW	
A97 How old was she when it was first diagnosed?	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar
A98 Did she ever have any other kind of cancer?	yes	no	yes	no	yes	no	yes	no	yes	no
A99 What kind of cancer did she have?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
A100 How old was she when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.

Father's Brothers (Paternal Uncles)

A101. Altogether, how many FULL brothers did your father have?_____(Number)
[ ] None

Father's Brothers	Oldest brother		2nd brother		3rd brother		4th brother		5th brother	
A102 Is your (?) father's brother still living	yes	no go to A104	yes	no go to A104	yes	no go to A104	yes	no go to A104	yes	no go to A104
A103 How old is he?	Age		Age		Age		Age		Age	
A104 How old was he when he died?	Age		Age		Age		Age		Age	
A105 Did he ever have Cancer?	[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW	
A106 What kind of cancer did he have? Types:	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Types:	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.
A107 How old was he when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Age	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.

Now I would like to ask questions about your children. Not adopted children, but your natural children.

Sons

A108. How many sons do you have? Natural sons, not adopted. _____ (Number)

Sons' Inform.	Oldest son		2nd son		3rd son		4th son		5th son	
A109 Is your (?) son still living	yes	no go to A111	yes	no go to A111	yes	no go to A111	yes	no go to A111	yes	no go to A111
A110 How old is he?	Age		Age		Age		Age		Age	
A111 How old was he when he died?	Age		Age		Age		Age		Age	
A112 Did he ever have Cancer?	[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW	
A113 What kind of cancer did he have? Types:	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Types:	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.
A114 How old was he when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Age	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.
A115 Was he a twin or triplet?	yes	no	yes	no	yes	no	yes	no	yes	no
A116 If yes, was he an identical or fraternal twin, triplet?	ident	frat	ident	frat	ident	frat	ident	frat	ident	frat

Daughters

A117. How many daughters do you have? Natural daughters, not adopted. _____

Daughter's Inform.	Oldest daughter		2nd daughter		3rd daughter		4th daughter		5th daughter	
A118 Is your (?) daughter still living	yes	no go to A120	yes	no go to A120	yes	no go to A120	yes	no go to A120	yes	no go to A120
A119 How old is she?	Age		Age		Age		Age		Age	
A120 How old was she when she died?	Age		Age		Age		Age		Age	
A121 Did she ever have Breast Cancer or Ovary Cancer?	[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW	
A122 How old was she when it was first diagnosed?	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar
A123 Did she ever have any other kind of cancer?	yes	no	yes	no	yes	no	yes	no	yes	no
A124 What kind of cancer did she have?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
A125 How old was she when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
A126 Was she a twin or triplet?	yes	no	yes	no	yes	no	yes	no	yes	no
A127 If yes, was she an identical or fraternal twin, triplet?	ident	frat.	ident	frat	ident	frat	ident	frat	ident	frat

COUSINS

A128. Do you have any cousins on your **father's** side of the family who have been diagnosed with cancer?

[ ] Yes
[ ] No
[ ] Don't Know

A129. Which of the following types of cancer have occurred in any of your cousins on your **father's** side of the family?

CANCER	OCCURRED
BREAST	
OVARY	
PROSTATE	
COLON	
OTHER_____	

A130. Do you have any cousins on your **mother's** side of the family who have been diagnosed with cancer?

[ ] Yes
[ ] No
[ ] Don't Know

A131. Which of the following types of cancer have occurred in any of your cousins on your **mother's** side of the family?

CANCER	OCCURRED
BREAST	
OVARY	
PROSTATE	
COLON	
OTHER_____	

B. REPRODUCTIVE HISTORY

B1. How old were you when you started having menstrual periods?

- ☐ Less than 12 years of age
- ☐ 12
- ☐ 13
- ☐ 14
- ☐ 15 years of age or older

B2. When did you have your last menstrual period?

- Less than one month ago
- Between one and six months ago
- Six months to one year ago
- More than one year ago

B3. What was your age at your last menstrual period?

Age ___

Subtract current age - above age = ___ - ___ = ___
If difference is five years or greater, skip to question B18.

B4. During the past five years, have you experienced changes in the length of your menstrual period, by this I mean the number of days of bleeding?

- ☐ Yes
- ☐ No

If No, skip to question B7

B5. Describe how the length of your menstrual period has changed in the past five years.

- ☐ Longer duration
- ☐ Shorter duration

B6. How many years ago did this change first occur?

- ☐ Within the past year
- ☐ 1-2 years ago
- ☐ 2-3 years ago
- ☐ 3-4 years ago
- ☐ 4-5 years ago

B7. During the past five years, have you experienced changes in the interval between your menstrual periods?

- ☐ Yes
- ☐ No

If No, skip to question B10

B8. Describe how the interval between your menstrual periods has changed in the past five years:

☐ Longer interval between periods
☐ Shorter interval between periods

B9. How many years ago did this change first occur?

☐ Within the past year
☐ 1-2 years ago
☐ 2-3 years ago
☐ 3-4 years ago
☐ 4-5 years ago

B10. During the past five years, have you experienced changes in the amount of bleeding you have with your menstrual cycles?

☐ Yes
☐ No
If No, skip to question B13.

B11. Describe how your periods have changed during this period:

☐ Heavier flow
☐ Lighter flow

B12. How many years ago did this change first occur?
Within the past year
☐ 1-2 years ago
☐ 2-3 years ago
☐ 3-4 years ago
☐ 4-5 years ago

B13. During the past five years, have you ever experienced hot flashes or night sweats?

☐ Yes
☐ No
If No, skip to question B16.

B14. How many years ago did this symptom first occur?

☐ Within the past year
☐ 1-2 years ago
☐ 2-3 years ago
☐ 3-4 years ago
☐ 4-5 years ago

B15. How often did you experience these symptoms?

____ times per week.
____ times per month.

B16. At present, are you still having menstrual periods?

☐ Yes
☐ No, skip to B18

B17. Please think back to your most recent menstrual period. How many days were there between your most recent period and the period before it? (Count from the first day of one bleeding period to the first day of the next bleeding period).

☐ Exactly ___ days
☐ About ___ days
☐ Do not know

Now skip to B19

B18. Why did you stop having your menstrual periods?

☐Periods stopped naturally

Surgery (check one):
- ☐Hysterectomy (uterus and both ovaries removed)
- ☐Hysterectomy (uterus and one/neither ovary removed)
- ☐Only ovaries removed
- ☐Surgery, but not sure which type

Other Treatments (Check all that apply)
- ☐Chemotherapy
- ☐Radiation therapy

☐Do not know
☐Other (please explain):_____

Now I am going to ask you about your use of hormone replacement therapy>

B19. Have you ever taken estrogen replacement therapy estrogen alone without progestins for conditions related to menopause or menstrual irregularities? **(see color cue card for drug identification and name.)**

☐ Yes
☐ No

B20. How old were you when you first used estrogen for this purpose?

☐☐ Age

B21. At the time you started to take this medication, how often were you having menstrual periods?

☐ Had not had a period for 12 or more months.
☐ Had at least one period in the previous 12 months, but cycles had become irregular.
☐ Periods were fairly regular during the previous 12 months.

B22. For how many years total have you taken estrogen alone for menopause or menstrual irregularities?

☐☐ Years

B23. Have you ever taken oral progestins **(see color cue card)**, either alone or in combination with estrogen, for conditions related to menopause or menstrual irregularities?

☐ Yes
☐ No

B24. How old were you when you first used progestins for this purpose?

☐☐ Age

B25. At the time you started to take this medication, how often were you having menstrual periods?

☐ Had not had a period for 12 or more months.
☐ Had at least one period in the previous 12 months, but cycles had become irregular.
☐ Periods were fairly regular during the previous 12 months.

B26. For how many years total have you taken progestins for menopause or menstrual irregularities?_____(YEARS)

B27. Since your diagnosis of breast cancer have you taken either estrogens or progestins

☐ yes
☐ no, skip to Section C

B28. What type of hormonal preparation have you taken?

☐ estrogen replacement therapy
☐ estrogen and progestin replacement therapy
☐ other _____(specify)
☐ Don't know

B29. Are you taking any of the following medications now?

☐ estrogen replacement therapy
☐ estrogen and progestin replacement therapy
☐ other _____(specify)
☐ Don't know

C. PREGNANCY AND FERTILITY

(Based on section B, if patient has children go to C2.)

Now I am going to ask you questions about your health. First, I would like to ask you about pregnancies you may have had and any medications you may have taken.

C1. Have you ever been pregnant?

☐ Yes
☐ No **(go to C19)**

C2. How many times, in total, have you been pregnant? (This includes live births, stillbirths, miscarriages, and induced abortions.) Number ☐☐

Now I would like to ask some specific questions about your pregnancies.

C3. What was the result of your (1st, 2nd, etc.) pregnancy? (PROBE: Was it a liveborn, still born, miscarriage or induced abortion?)

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Livebirth				
Stillbirth				
Miscarriage				
Abortion				
Multiple				
Pregnant now				
Don't Know				

C4.How many weeks or months did your pregnancy last?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Weeks				
Months				
Full Term				
Early				
Late				
Don't Know				

C5. In what month and year did this pregnancy end?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Month/year				

LIVEBORN ONLY:

C6. Was it a boy or a girl?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Boy				
Girl				
Twin Girls				
Twin Boys				
Twin girl/boy				
other mult.				

LIVEBORN ONLY:

C7. What was the baby's birthweight?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Birthweight Lbs/oz				

C8. Did you breastfeed this(these) child(ren) for 2 weeks or longer?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Yes				
No				

C9. How long did you breastfeed this (these) child (ren)?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Weeks				
Months				
Years				
Still Nursing				

C10. Did you try for 12 months or more to become pregnant for this pregnancy?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Yes				
No				

C11. Did you take fertility drugs to become pregnant for this pregnancy?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Yes				
No				

C12. What was the name of the fertility drug?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Medication				
Don't Know (check)				

C13. For how many weeks or months prior to this pregnancy did you take it?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Weeks				
Months				
Don't Know				

C14. Did you take medication to prevent miscarriage or "hold" this pregnancy?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Yes				
No				

C15. What was the name of the medication?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Medication				
Don't Know (check)				

C16. How many weeks pregnant were you when you started taking the medication?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Weeks				
Months				
Early				
Late				
Don't Know				

C17. How many weeks or months during this pregnancy did you take it?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Weeks				
Months				
Don't Know				

C18. Since your last pregnancy, have you tried for twelve months or more to become pregnant, but were unable to?

[ ] Yes
[ ] No

Now skip to Question C25

C19. Was there ever a time in your life when you tried for at least 12 months to become pregnant without being able to?

[ ] Yes
[ ] No

C20. Have you ever taken fertility drugs, such as Clomid or Perganol, to stimulate ovulation?

[ ] Yes
[ ] No, skip to C27

C21. What was the name of the medication?

	1ST Medication	2ND Medication	3RD Medication	4TH Medication
Medication				
Don't Know				

C22. In what month and year did you start taking it?

	1ST Medication	2ND Medication	3RD Medication	4TH Medication
Medication				
Month/Year				

C23. For how many months or weeks did you take it?

	1ST Medication	2ND Medication	3RD Medication	4TH Medication
Medication				
Months				
Weeks				

C24. Did you take fertility drugs after that? [ ] Yes **(Return to C21 for up to 4 Meds)**
[ ] No

C25. Did you or your husband or partner ever have tests done for fertility?

[ ] Yes
[ ] No, go to C27

C26. Did the doctor say the problem was related to you, your husband or partner, or both of you?

[ ] Self
[ ] Husband/partner
[ ] Both
[ ] No problem
[ ] Doctor didn't know
[ ] Don't know

C27. Have you ever taken birth control pills for any purposes?

[ ] Yes **If "Yes," proceed with questions.**

[ ] No **If "No," please go to C35.**

C.28 For what purpose did you take birth control pills? (Check all that apply.)
[ ] Birth Control
[ ] Regulate menstrual cycles
[ ] other purpose_____

C29. How old were you when you first began taking birth control pills?

☐☐Age

C30. Are you currently taking birth control pills?

☐ Yes ☐ No

C31. Keeping in mind that you may have started and stopped several times, for a total of how many years or months did you take birth control pills?

☐ Less than one year
☐ 1 - 3 years total
☐ 4 - 5 years total
☐ 6 - 10 years total
☐ 11 - 15 years total
☐ 16 or more years total

C32. In what month and year did you (first/next) begin to use them?

	1ST Pill use	2ND Pill use	3RD Pill use	4TH Pill use
Month/Year				
Don't Know				

C33. What was the name of the pill you used?

	1ST Pill use	2ND Pill use	3RD Pill use	4TH Pill use
Name				
Don't Know				

C34. How long did you take them continuously this time?

	1ST Pill use	2ND Pill use	3RD Pill use	4TH Pill use
Months				
Years				
Less than 1 mos				
Don't know				

After question C34 skip to C36.

C35. What was the main reason you never used birth control pills?

(CHECK ALL THAT APPLY)
[ ] Doctor recommended against
[ ] Respondent concerned about family history
[ ] Respondent concerned about general safety
[ ] Personal choice, or no need

C36. Are there any other hormone medications that you ever took for any reason, other than those we have already discussed, including **thyroid** medication?

[ ] Yes
[ ] No

C37. What was the name of the medication?

_____
[ ] Don't know

C38. For what reason were you taking this medication?

_____

C39. In what month and year did you start taking it?

__/__

C40. For how many months did you take it? ____

C41. Have you had any pregnancies since you were diagnosed with Breast Cancer?

☐ Yes
☐ No

C42. What was the outcome?

	1ST PREG	2ND PREG	3RD PREG	4TH PREG
Livebirth				
Stillbirth				
Miscarriage				
Abortion				
Muluple				
Pregnant now				
Don't Know				

D. MEDICAL HISTORY

Now I would like to ask you some more questions about your health.

D1. Did a doctor every tell you that you had any of the following conditions:

CONDITIONS:	YES	AGE WHEN FIRST TOLD OF CONDITION
Gallstones or gallbladder disease		
Endometriosis or Endometrioma		
Diabetes		
Colon polyps (Probe: polyps in the colon		
Uterine fibroids		
Ovarian cyst or cystic ovaries		
High blood pressure (not during pregnancy		
High cholesterol		
Renal Disease or Chronic UTI		
Thyroid Disease		

Now I would like to ask you about some procedures that you may have had in the past. I am going to ask you about procedures prior to your recent diagnosis of breast cancer.

D2. In the past, prior to your recent diagnosis of breast cancer, did a doctor ever tell you that you had fibrocystic breast disease?

[ ] Yes
[ ] No (skip to D4)

D3. How old were you the first time you were told this?

__
Age

D4. In the past, prior to any procedures performed as part of your current diagnosis and treatment for breast cancer, did you ever have a breast biopsy or breast aspiration?

[ ] Yes
[ ] No (skip to D8)

D5. What was the reason for the breast biopsy or aspiration?

☐ To follow an abnormal mammogram
☐ To check a lump detected by you
☐ To check a lump detected by your physician

☐ Other_____

D6. In what year was this done?

☐☐☐☐(year)

D7. What was found?

☐ Normal breast tissue
☐ Mastitis
☐ Benign breast disease, including fibrocystic disease
☐ In-situ carcinoma

☐ Other _____

D8. Prior to your diagnosis of breast cancer, did you ever have any surgery that changed the size or shape of your breasts?

[ ] Yes
[ ] No, skip to D11

D9. How old were you when you had this surgery?

__
Age

D10. Which procedure was used? (PROBE)

[ ] PROPHYLACTIC MASTECTOMY
[ ] BIOPSY/LUMPECTOMY
[ ] BREAST PROSTHESIS INSERTED (AUGMENTATION)
[ ] COSMETIC REDUCTION
[ ] OTHER _____

D11. Now I would like to ask you a few questions about your current diagnosis and treatment for breast cancer. In what month and year were you given this most recent diagnosis?

__/__
(month) (year)

D12. Was this cancer diagnosed in your left, right, or both breasts?

[ ] LEFT ONLY
[ ] RIGHT ONLY
[ ] BOTH
[ ] DON'T KNOW

D13. How was this breast cancer discovered: did you first notice a problem, was it found during a routine mammogram, or did you doctor notice a problem?

[ ] SELF-DETECTED
[ ] MAMMOGRAPHY-DETECTED
[ ] PHYSICIAN-DETECTED
[ ] OTHER: _____
[ ] DON'T KNOW

I am now going to ask you some questions about screening mammograms. I would like to know about mammograms performed in the past, before any mammograms performed as part of your recent diagnosis of breast cancer.

D14. Did you have mammograms before the age of forty?

____ Yes, go to D15
____ No, go to D16
____ Don't know, go to D16

D15. How many screening mammograms total did you have prior to age 40?

____ Number
____ Don't know

D16. How often did you have mammograms between the ages of 40 and 50?

☐ More that once per year
☐ Once per year
☐ Once every two years
☐ Less than once every two years
____Never screened
____Not applicable (patient younger than age 40)

D17. How often did you have mammograms between the ages of 50 and 60?

☐ More that once per year
☐ Once per year
☐ Once every two years
☐ Less than once every two years
____Never screened
____ Not applicable (patient younger than age 50)

D18. Is this most recent diagnosis of breast cancer the first time that you have ever had cancer?

[ ] Yes, go to Section E.
[ ] No

D19. Please tell me what type(s) of cancer you have had in the past, including skin and all other cancers, and your age at diagnosis.

Type of Cancer	a	b	c	d
Age at Diagnosis	a	b	c	d

E. SMOKING

E1. Have you smoked at least 100 cigarettes, that is 5 packs or more, in your lifetime?

☐Yes (if yes, go to E2)
☐No (if no, skip to section F)

E2. How old were you when you started smoking cigarettes?

☐☐Age

E3. Do you smoke cigarettes NOW?

☐Yes (if yes, go to E5).
☐No

E4. How old were you when you stopped smoking cigarettes?

☐☐Age

E5. At the PRESENT TIME, on average how many packs of cigarettes do you smoke per day?

☐Less than ONE pack per day
☐ONE to TWO packs per day
☐More than TWO packs per day

E6. In the PAST, during the years in which you smoked regularly, on average how many cigarettes did you smoke per day?

☐Less than ONE pack per day
☐ONE to TWO packs per day
☐More than TWO packs per day

E7. During the time following your recent diagnosis of breast cancer, on average how many cigarettes have you smoked per day?

☐ None
☐Less than ONE pack per day
☐ONE to TWO packs per day
☐More than TWO packs per day

E8. Have you ever smoked a cigar or pipe regularly?

☐Yes (if yes, go to E9)
☐No (if no, go to section F)

E9. How old were you when you started smoking a cigar or pipe?

☐☐Age

E10. How old were you when you stopped smoking a cigar or pipe?

☐☐Age

E11. Do you smoke a cigar or pipe NOW?

☐Yes (if yes, go to E5).
☐No (if no, skip to E6).

E12. Since your recent diagnosis of breast cancer, how often have you smoked a cigar or pipe?
☐Less than once a day
☐Once or twice a day
☐More than twice a day

F. HEIGHT, WEIGHT, PHYSICAL ACTIVITY

Now I have some questions about your weight and level of physical activity in the past ten years.

F1. What has been your lowest weight in the past ten years, not counting this past year?

___lbs
[ ] Don't know

F2. How old were you (during the past ten years) when weighed that amount?

___ yrs old
[ ] Don't know

F3. What is the most that you ever weighed during the past ten years? (PROBE: Do not include any times you were pregnant or nursing.)

___lbs
[ ] Don't know

F4. How old were you (during the past ten years) when you weighed this amount?

___ yrs old
[ ] Don't know

F5. When you gain weight, where on your body do you tend to gain it most easily: below the waist, around and above the waist, or above and below the waist equally? (PROBE: Do not include times when you were pregnant.)

[ ] BELOW THE WAIST
[ ] AROUND AND ABOVE THE WAIST
[ ] ABOVE AND BELOW WAIST EQUALLY
[ ] NEVER CARRIED EXTRA WEIGHT

F6. For the past FIVE years prior to your recent diagnosis of breast cancer, please tell me whether you participated regularly in the following activities: (By "regularly" we mean at least 2 hours per week spent in each activity). **(Check all that apply)**

[ ] Engaged in heavy manual work, such as digging or chopping with tools, farm or ranch work, construction, scrubbing floors, etc.

[ ] Participation in a sports team, including attendance at practice sessions.

[ ] Participation in individual sports, such as racquet sports, swimming, gymnastics, running/jogging, race walking, bicycling, horseback riding, dance or excercise classes, martial arts.

[ ] Engaged in brisk walking or stair climbing as a part of your work or home activities.

[ ] Participation in light physical activities, such raking lawns, light household chores, walking for pleasure, bowling, golf.

[ ] Other: (explain)

F7. I would like to ask about your participation in these same activities since your recent diagnosis of breast cancer. Since that time, please tell me whether you participated regularly in the following activities: (Again, by "regularly" we mean at least 2 hours per week spent in each activity). **(Check all that apply)**

[ ] Engaged in heavy manual work, such as digging or chopping with tools, farm or ranch work, construction, scrubbing floors, etc.

[ ] Participation in a sports team, including attendance at practice sessions.

[ ] Participation in individual sports, such as racquet sports, swimming, gymnastics, running/jogging, race walking, bicycling, horseback riding, dance or excercise classes, martial arts.

[ ] Engaged in brisk walking or stair climbing as a part of your work or home activities.

[ ] Participation in light physical activities, such raking lawns, light household chores, walking for pleasure, bowling, golf.

[ ] Other: (explain)

G. ALCOHOL USE

Now I am going to ask you about your consumption of alcoholic beverages.

ALCOHOLIC BEVERAGES include beer, wine and liquor.

G1. In the past five years, have you had at least 12 drinks of any alcoholic beverage?

☐Yes (if yes, go to G2)
☐No (if no, skip to section H)

G2. In the past five years, PRIOR your recent diagnosis of breast cancer, did you consume alcoholic beverages at least once a week?

☐Yes (if yes, go to G3)
☐No (if no, skip to G5)

G3. During this time on how many days did you consume alsoholic beverages in an average week?

_____number
____Don't Know

G4. On the days when you drank alcoholic beverages, how many drinks did you have in a single day, on AVERAGE?

_____number
____Don't Know

G5. Were there any times when you drank more than five drinks of alcohol in a single day?

____yes (go to G6)
____no (go to G7)

G6. In the five years prior to your diagnosis of breast cancer, how many days total did you have more than five drinks in a single day?

_____number
_____Don't Know

Now I am going to ask you about your consumption of alcohol since your recent diagnosis of breast cancer.

G7. Since your recent diagnosis of breast cancer, have you consumed alcoholic beverages at least once a week?

____yes (go to G8)
____no (go to G10)

G8. In an average week, on how many days do you consume alcoholic beverages?
_____number
_____ Don't Know

G9. On the days when you drink alcoholic beverages, how many drinks do you have in a single day on AVERAGE?

_____number
_____Don't Know

G10. Since your recent diagnosis of breast cancer are there any times when you had more than five drinks of alcohol in a single day?

____Yes, Go to G11
____No, Go to section H

G11. Since your recent diagnosis of breast cancer, on how many days have you had more than five drinks of alcohol in a single day?

_____Number
_____Don't Know

H. MEDICATION HISTORY

I am going to ask about some medications you may have taken in the past and may be taking now.

H1. The following table refers to over-the-counter and prescription medications.

In the past five years, PRIOR to your recent diagnosis of breast cancer have you taken any of the following medications on a regular basis? By this we mean three times a week or more for at least one month.

Aspirin or buffered aspirin: Bayer, Anacin, Bufferin, Ascriptin	Yes	No
Ibuprofen: Advil, Nuprin, Motrin IB; Naproxin: Alleve	Yes	No
Prescription anti-inflammatory drugs: Motrin, Feldene, Voltarin, Clinoril, Indocin	Yes	No
Acetaminophen: Tylenol, Panadol, Anacin-3, Dristan AF, Comtrex	Yes	No
BC, Goodys, Emprin, APC powders	Yes	No
Excedrin or Vanquish	Yes	No
Antidepressants or anti-anxiety medications: Prozac, Zoloft, Elavil, Valium, Librium, Xanax, other	Yes	No

H2. Since your recent diagnosis of breast cancer have you taken any of the following medications on a regular basis? By regular we mean three times a week or more.

Aspirin or buffered aspirin: Bayer, Anacin, Bufferin, Ascriptin	Yes	No
Ibuprofen: Advil, Nuprin, Motrin IB; Naproxin: Alleve	Yes	No
Prescription anti-inflammatory drugs: Motrin, Feldene, Voltarin, Clinoril, Indocin	Yes	No
Acetaminophen: Tylenol, Panadol, Anacin-3, Dristan AF, Comtrex	Yes	No
BC, Goodys, Emprin, APC powders	Yes	No
Excedrin or Vanquish	Yes	No
Antidepressants or anti-anxiety medications: Prozac, Zoloft, Elavil, Valium, Librium, Xanax, other	Yes	No

H3. Which of the following medications do you take on a regular basis NOW? By regular we mean three times a week or more.

Aspirin or buffered aspirin: Bayer, Anacin, Bufferin, Ascriptin	Yes	No
Ibuprofen: Advil, Nuprin, Motrin IB; Naproxin: Alleve	Yes	No
Prescription anti-inflammatory drugs: Motrin, Feldene, Voltarin, Clinoril, Indocin	Yes	No
Acetaminophen: Tylenol, Panadol, Anacin-3, Dristan AF, Comtrex	Yes	No
BC, Goodys, Emprin, APC powders	Yes	No
Excedrin or Vanquish	Yes	No
Antidepressants or anti-anxiety medications: Prozac, Zoloft, Elavil, Valium, Librium, Xanax, other	Yes	No

H4. Are there any other medications that you are currently taking for any reason?

☐ Yes
☐ No

H5. Information on medications currently taking, excluding any cancer therapeutic drugs. (Probe: Heart, Kidney, Diabetes, Chronic UTI, Topical steroids, Theophylines, OTC use.)

	First Med	Second Med	Third Med	Fourth Med
Name of med.				
Reason for taking med				
In what month and year did you start taking the med				
For how many months did your take it				

I. VITAMIN SUPPLEMENT HISTORY

NOW I AM GOING TO ASK YOU SOME QUESTIONS ABOUT DIETARY SUPPLEMENTS AND VITAMINS. I WANT TO KNOW IF YOU TOOK OR ARE NOW TAKING THESE SUPPLEMENTS ON A REGULAR BASIS. BY A REGULAR BASIS I MEAN AT LEAST TWO TIMES PER WEEK.

Supplement	Over the past 5 years, PRIOR to your recent diagnosis of breast cancer, did you take any of the following dietary supplements?		Do you take any of the following dietary supplements now?	
Vitamin A	Yes	No	Yes	No
Vitamin C	Yes	No	Yes	No
Vitamin E	Yes	No	Yes	No
Beta-carotene	Yes	No	Yes	No
Selenium	Yes	No	Yes	No
Iron	Yes	No	Yes	No
Calcium or dolomite	Yes	No	Yes	No
Zinc	Yes	No	Yes	No
Cod Liver Oil	Yes	No	Yes	No
Vitamin B12 or B Complex	Yes	No	Yes	No
Folate or Folic Acid	Yes	No	Yes	No
Multivitamin or Multivitamin with Iron	Yes	No	Yes	No

J. DIETARY HISTORY

J1. Over the past five (5) years, prior to your recent diagnosis of breast cancer, how often did you eat the following types of foods? (Place "X" in the appropriate boxes.)

Type of food	Never or less than once a week	Once a week	3-4 times a week	Once every day	Twice a day or more
Hamburger or cheeseburger					
Beef steaks					
Chicken					
Pork chops or Ham Steak					
Lamb chops					
Bacon or Breakfast Sausage					
Hot dogs or luncheon meat					
Fish					
Fruits and Vegetables					
Grains (pastas, rice, breads, etc.)					
Dairy (milk, cheese, ice cream, etc.)					

J2. How often do you eat these foods now?

Type of food	Never or less than once a week	Once a week	3-4 times a week	Once every day	Twice a day or more
Hamburger or cheeseburger					
Beef steaks					
Chicken					
Pork chops or Ham Steak					
Lamb chops					
Bacon or Breakfast Sausage					
Hot dogs or luncheon meat					
Fish					
Fruits and Vegetables					
Grains (pastas, rice, breads, etc.)					
Dairy (milk, cheese, ice cream, etc.)					

J3. Do you currently follow a **vegetarian** diet?
This means you do not consume beef, pork, lamb, poultry or fish.

☐ Yes
☐ No

J4. Over the past five years, did you follow a **vegetarian** diet for a period of one year or more?

☐ Yes
☐ No

K. OCCUPATION AND RESIDENTIAL HISTORY

Those are all my questions about your health and your family. My final questions are about jobs that you may have ever had as an adult and where you have lived during your lifetime.

K1. Where were you born? _____State

K2. What kind of community did you spend most of your life when you were:

Location	Less than 18 years old	18-25 years old	Greater than 25 years old
Large city (pop.>100,000			
Suburb of large city			
Town or city (pop.50,000-100,000)			
Town (pop.<10,000)			
Rural, non-farm (in the country, but not a farm)			
On a farm			
Don't remember			

K3. Have you ever been employed outside the home?

1[ ] Yes
2[ ] No

K4. When you were employed outside the home, what was the occupation you held for the LONGEST PERIOD OF TIME? (PROBE: What was your complete job title?)

_____(TITLE)

K5. At what age did you start working at this job?_____AGE_____

K6. How many years total did you work at this job?_____ (years)

K7. What was the occupation that you held FOR THE SECOND LONGEST PERIOD OF TIME?_____(TITLE)

K8. At what age did you start working at this job?_____(AGE)

K9. How many years total did you work at this job?_____(YEARS)

K10. What was the occupation that you held FOR THE THIRD LONGEST PERIOD OF TIME?_____(TITLE)

K11. At what age did you start working at this job?_____(AGE)

K12. How many years total did you work at this job?._____(years)

K13. IN ADDITION TO THE INFORMATION YOU HAVE PROVIDED, have you worked in the following professions?

OCCUPATION	yes/no	how many years	age at start
Radiology Technician			
Dental Technician			
Veterinary Technician			
Veterinarian			
Medical Doctor			
Dentist			
Laboratory Worker			
Nurse			
Beautician/Hairdresser			
Airline Stewardess			
Managerial/Clerical Worker			

K14. Have you ever worked night shifts in any of your job positions?

☐ Yes
☐ No
How many years total? _____

K15. Have your ever lived or worked on a farm?

☐ Yes
☐ No
How many years total did you live or work on farm? _____

K16. Did you ever mix or apply pesticides or herbicides as part of your job?

☐ Yes
☐ No

K17. Did you ever use pesticides or herbicides in your private garden?

☐ Yes
☐ No

K18. Did you ever use pesticides inside your home? This includes control of roaches, ants, termites, etc.

☐ Yes
☐ No

K19. Did your ever use pesticides on your pets or livestock? This includes flea and tick control products?

☐ Yes
☐ No

K20. Where was this phone interview conducted?

☐ Home
☐ Office
☐ Relative's House
_____ Relative
☐ Other
_____ Where?

K21. Before we end the interview, do you have any comments about the interview or is there anything you would like to add that was not covered by the interview?

_____
_____
_____
_____

K22. Do you have any opinions as to what caused or influenced your breast cancer occurrence? Please feel free to give you feelings about this matter? (Refer to comments from self-administered questionnaire.)

_____
_____
_____
_____

L. END OF INTERVIEW

L1. Thank you very much for your help in our survey. Your answers will be very helpful in our research. May we contact you again if we need additional information?

[ ] Yes
[ ] No, skip to M1.

L2. Could you provide me with the name, address, and phone number of someone who will always know where to get in touch with you?

_____ NAME
_____ ADDRESS
_____
_____ PHONE

L3. With your permission we would like to send you another questionnaire concerning your personal well-being.

[ ] Yes
[ ] No
[ ] Undecided or will let us know

L4. We would like to have your address to mail the questionnaire:

_____ NAME
_____ ADDRESS
_____
_____ PHONE

We will mail you the questionnaire with instructions and will contact you by phone to arrange for a convenient time to obtain your responses.

L5. Thank you again.

END CALL AND RECORD RESULT CODE AND TIME ENDED ON QUESTIONNAIRE COVER

M. INTERVIEWER REMARKS

M1. Were other people present in the room with the patient during the interview?

- ☐ Yes, the whole time
- ☐ Yes, for part of the time
- ☐ No

M2. Respondent's cooperation was:

- ☐ Very Good
- ☐ Good
- ☐ Fair
- ☐ Poor
- ☐ Other (Specify)_____

M3. The quality of the responses was:

- ☐ High quality
- ☐ Generally reliable
- ☐ Questionable
- ☐ Unsatisfactory
- ☐ Other (Specify)_____

M4. The respondent:

- ☐ Recalled all information
- ☐ Had trouble with amounts or frequencies
- ☐ Had trouble with dates
- ☐ Had trouble recalling overall
- ☐ Other (Specify)_____

M5. If respondent had difficulty recalling, the reasons for unsatisfactory or questionable information is indicated below:

- ☐ Did not want to be more specific
- ☐ Did not understand or speak English well
- ☐ Was bored or uninterested
- ☐ Was upset, depressed or angry
- ☐ Had poor hearing or speech
- ☐ Was confused or distracted by frequent interruptions
- ☐ Was inhibited by others around her
- ☐ Was embarrassed by the subject matter
- ☐ Was emotionally unstable
- ☐ Was physically ill
- ☐ Became tired and began to not answer or understand as well as early on due to length of questionnaire
- ☐ Other (Specify)

_____

_____

_____

APPENDIX III

CALGB Policy Governing Genetic Studies

CALGB POLICIES GOVERNING GENETIC STUDIES

Whereas studies of somatic mutations in cancer cells pose little risk to the patient, studies of heritable cancer genes may lead to discrimination by insurers and employers. In addition, the discovery of a familial cancer gene carries with it psycho-social consequences which are only imperfectly understood at present and which add to the above risk. For this reason, all consents for studies of heritable cancer genes must be obtained prospectively. These consents should provide adequate information to allow the patient to assess the risk of participation in the study, and should indicate the steps that CALGB is taking to reduce such risks.

Banked material, already obtained from patients on CALGB protocols may be used for studies of heritable genes, but in this case, a reconsent must be obtained from the patient.

The CALGB will take steps to secure, if possible, a Certificate of Confidentiality from the NIH in order to reduce the risk that disclosure of patient identifiers along with information about gene studies will occur.

CALGB will ask its investigators to advocate the passage of state laws preventing insurers and employers from asking for any information about whether the person has had a diagnosis of cancer or whether the person or family members have been the subject of genetic testing.

Because it is unknown what tests may be appropriate on specimens during the time the specimen is banked, the patient will be asked to grant a broad permission for testing. The patient will be informed that heritable gene studies will be limited to those relevant to cancer. The patient will not be asked to grant permission for each individual laboratory study to be performed. Instead, the patient will be assured that all laboratory investigators will have had their project approved by their respective institutional review board prior to receiving permission to study their tissue.

Access to the tissue bank will be granted upon the recommendation of the appropriate committee overseeing the bank. Each investigator using the bank will provide a written description of the project for which the bank is to be used and will be limited to that project. The investigators must agree that all data resulting from their studies will be furnished to the Data Management Center for entry into the CALGB data base. This agreement will also contain provisions for maintaining patient confidentiality. Clinical information from the CALGB data base will not be provided to users of the bank, except in reports prepared by the CALGB which will lack patient identifiers.

Each protocol describing studies of heritable cancer genes will define optimal patient support and set minimum limits for the level of genetic counseling that must be in place in each institution to allow protocol activation.
The CALGB will establish a committee responsible for review of studies involving heritable cancer genes. The charge to this committee is to consider the short and long-term risks associated with protocols involving studies of heritable genes and to advise the Chair with respect to the appropriate actions concerning these studies. The committee is also responsible for reviewing the resources available for genetic counseling at CALGB member institutions and approving these programs as a requisite for institutional participation in designated protocols. This committee will be comprised of CALGB members as well as representatives of the public.

APPENDIX IV

DHHS Confidentiality Certificate

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Washington D.C. 20201

JUN 24 1996

Karen Sartell, M.A.
Cancer and Leukemia Group B
Central Office of the Chairman
208 South LaSalle Street, Suite 2000
Chicago, IL 60604-1104

Dear Ms. Sartell:

I am happy to send you the certificate of confidentiality for the research project "Cancer and Leukemia Group B -- Linkage of Molecular and Epidemiological Breast Cancer Investigations with Treatment Data: A Specialized Registry."

Please be sure that the informational statement given to participants accurately states the intended uses of personally-identifiable information and the confidentiality protections, including the protection provided by the certificate of confidentiality, with its limitations and exceptions.

May I ask that you advise me of any situation in which the certificate is employed to resist disclosure of information in legal proceedings. I am at 440D Humphrey Building, telephone (202) 690-5896 (direct dial, sometimes answered by machine) or (202) 690-7100, telefax (202) 690-5882. Internet: jfanning@osaspe.dhhs.gov.

If attorneys for the University wish to discuss the use of the certificate, they may contact the Chief Counsel of the Public Health Service, Mr. Richard Riseberg, at (301) 443- 2644.

If you have any questions, or if we can otherwise help, please call.

Sincerely yours,

John P. Fanning
Senior Policy Analyst
Division of Data Policy
Office of Program Systems

CONFIDENTIALITY CERTIFICATE

issued to

Employees of

Cancer and Leukemia Group B
and All Participating Institutions

and Other Participants

conducting research known as

LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

In accordance with the provisions of section 301(d) of the Public Health Service Act (42 U.S.C. § 241(d)) this certificate is issued to protect the privacy of research subjects by withholding their identities from all persons not connected with the research.

Under authority vested in the Secretary of Health and Human Services under that section, all persons who --

(1) are employed by Cancer and Leukemia Group B, and all participating institutions, and their contractors and cooperating agencies; and

(2) have, in the course of that employment, access to the information which would identify individuals who are the subjects of a research project entitled "Linkage of Molecular and Epidemiological Breast Cancer Investigations with Treatment Data: A Specialized Registry"

are hereby authorized to protect the privacy of the individuals who are the subjects of that research by withholding their names and other identifying characteristics from all persons not connected with the conduct of that research, with the exceptions and limitations set forth below.

The purpose of this research project is to collect breast tissue, plasma and urine from cancer patients; review and confirm the histopathological diagnosis of breast cancer on submitted tissue; gather key family, endocrine and reproductive history, and exposure data, on subjects; and provide specimens to approved investigators for study, and receive results of these studies.

As provided in section 301(d) of the Public Health Service Act (42 U.S.C. § 241(d)),

> "Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals."

The following conditions apply to the protection provided under this certificate:

(1) This certificate does not authorize the Cancer and Leukemia Group B, participating institutions, or their contractors or cooperating agencies to refuse to reveal identifying information concerning research subjects if any of the following conditions exist:

(a) The subject (or, if he or she is legally incompetent, his or her guardian) consents in writing to disclosure of identifying information.

(b) Authorized personnel of the United States Department of Health and Human Services or of the U.S. Army Medical Research and Materiel Command request such information for audit or program evaluation of the research project, or for investigation of the Cancer and Leukemia Group B, participating institutions, or their contractors or employees in carrying out the research project.

(c) Release is required by the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §§ 301 et seq.) or regulations promulgated thereunder (Title 21, Code of Federal Regulations).

(2) This certificate requires that there be no disclosures of identifying characteristics of research subjects in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to compel disclosure of the identifying characteristics of research subjects, except as provided for in paragraph (1), above.

(3) The confidentiality certificate does not govern the voluntary disclosure of identifying characteristics of research subjects.

(4) This certificate does not represent an endorsement of the research project by the Department of Health and Human Services.

(5) All research subjects in the project will be given a fair, clear explanation of the protection this certificate affords, and of the limitations and exceptions to the protection.

(6) This certificate is effective upon issuance, and will expire at the end of June 2011 or sooner if the holder is notified of cancellation in accordance with the procedures set out in 42 C.F.R. § 2a.8. The protection afforded by this certificate of confidentiality is permanent (including after death) for persons who participated as subjects in the research during any time the certificate was in effect.

Date: JUN 19 1996

Philip R. Lee, M.D.
Assistant Secretary for Health

CALGB CONFIRMATION OF REGISTRATION

CALGB 9484: LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

IRB Approval ___/___/___

☐☐☐☐☐ CALGB Patient Number

Consent Form ___/___/___

☐☐☐☐ Institution/Adjunct _____/_____

☐☐☐☐ Physician of Record _____

Provider of Information/Phone _____

☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ Patient Name (l,f,m.i.)

☐☐☐☐☐☐☐☐☐☐ Hospital Chart #

☐☐☐☐☐☐☐☐☐ Social Security #

Prior CALGB Protocols (1-No,2-Yes) If yes, list protocols: _____

☐☐ Race

(1-White,2-Hispanic,3-Black,4-Oriental,5-Native Hawaiian,6-Native American,7-Indian,8-Filipino,9-Other, 10-Patient refusal,11-Institution refusal,-1-Unknown)

☐ Sex (1-M,2-F)

☐☐ ☐☐ ☐☐☐☐ Birthdate

M D Y

☐☐☐☐☐ - ☐☐☐☐ Zip Code

Diagnosis_____ ☐☐ ☐☐ ☐☐☐☐ Date of Diagnosis

M D Y

ELIGIBILITY CRITERIA-See Section 4.0

_____ Does the institution have a genetic counseling program or committed to developing a program within a few years? (1 -no; 2 -yes)

_____ Patient Eligible? (1-no; 2-yes, all requirements confirmed)

_____ Is the patient registered to a CALGB breast protocol listed in section 4.1?

PATIENT CONTACT INFORMATION

Patient's phone number _____

SPECIMEN INFORMATION

_____ Has patient consented to release rights to specimens? (1-no; 2-yes)

_____ Have the pre-treatment samples been submitted? (1-no; 2-yes)

☐☐ ☐☐ ☐☐☐☐ Date of Registration

M D Y

_____

Registrar 6/19/97

Genetic Testing in Breast Cancer Cooperative Clinical Trials

Barriers and Opportunities

Robert C. Millikan,[a,b] Alice B. Kornblith,[c] O. Ross McIntyre,[d] Donald A. Berry,[e] Gloria J. Broadwater,[e] Dale P. Sandler,[f] Kathy Karas,[g] Lynn Dressler,[a] Laura S. Gross,[e] Deborah E. Collyar,[h] Richard L. Schilsky[g]

Introduction In 1994, the cooperative cancer clinical trials group, Cancer and Leukemia Group B (CALGB), set up a registry to collect genetic and epidemiologic information from patients undergoing treatment for breast cancer. The primary goal of the registry is to investigate the predictive and prognostic value of germline mutations in cancer susceptibility genes (e.g., BRCA1, BRCA2).

Methods Patients from ongoing CALGB treatment trials are eligible for participation in data collection for the registry. The registry collects reproductive, dietary, and exposure history; germline DNA; and somatic DNA from tumor blocks. Information from laboratory assays (including genetic tests) is linked to the CALGB clinical database, which contains treatment and follow-up information.

Results Of 883 patients entered onto four CALGB treatment protocols, only 43 patients were enrolled in the registry during the first year of accrual. The majority of CALGB institutions did not approve the registry protocol because of ethical and legal concerns about the confidentiality of genetic information. Patient informed consent presented significant challenges for both oncologists and patients. We implemented procedures to address these concerns. Although enrollment increased slightly, the number of patients in the registry remains far below our expectation.

Discussion Patient confidentiality and informed consent present major obstacles for genetic studies conducted among cooperative groups. We present a series of recommendations for future projects that explore the role of genetic factors in cancer treatment. Consensus will be needed on several key issues, especially disclosure of genetic test results, informed consent, and patient confidentiality, if such projects are to go forward (*Cancer Therapeutics* 1998;1:96–100).

Key words Breast cancer, Genetic testing

It is now possible to identify carriers of germline mutations in BRCA1 (1–2), BRCA2 (3), and other cancer susceptibility genes. Estimating risk of breast and ovarian cancer for women with BRCA1 and BRCA2 mutations, particularly women who are not members of high-risk families, has been the focus of intensive research (4–6). However, the clinical significance of gene-carrier status for women already diagnosed with breast cancer is also an important area of investigation. Porter et al. (7) observed that 5-yr survival time in breast cancer patients from BRCA1-linked pedigrees was significantly greater than the survival time of breast cancer patients in general. A similar outcome for such patients with ovarian cancer was also reported by Rubin et al. (8). However, other researchers have reported that the histology and grade of breast tumors from BRCA1 and BRCA2 carriers may be associated with a worse prognosis (9–12). Because comparisons of breast cancer patients with comparable stage disease and treatment were not performed in these studies, it is impossible to determine whether gene carriers have a better or worse prognosis than patients with sporadic disease. Similarly, to determine whether germline mutations in BRCA1 or BRCA2 serve as predictive factors (indicators of patients most likely to respond to specific forms of therapy), a comparison must be made in which carriers and noncarriers receive defined forms of treatment and follow up is actively pursued. Such studies are best conducted within the context of clinical trials (13–14).

To support research aimed at identifying prognostic and predictive indicators among breast cancer patients, investigators from Cancer and Leukemia Group B (CALGB) set up a registry to collect and integrate genetic, epidemiologic, and clinical information on patients receiving therapy specified by the treatment protocols of the group. For a potential use of the registry, we were particularly interested in the effects of dose escalation for adjuvant chemotherapy and radiation among BRCA1 and BRCA2 carriers. We describe here

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the development of the project as well as obstacles encountered, and offer recommendations on how to conduct similar studies in the future.

METHODS

In 1993, CALGB obtained funding from the Department of Defense, United States Army Research and Materiel Command, for a project called Linkage of Molecular and Epidemiological Breast Cancer Investigations with Treatment Data: A Specialized Registry. Patients enrolled on four ongoing CALGB breast cancer treatment protocols were eligible for concurrent entry onto the registry: CALGB 9082 (High Dose Combination Chemotherapy for Patients with stage II or III Breast Cancer), 9342 (Taxol for Metastatic Breast Cancer), 9343 (Lumpectomy, Radiation and Tamoxifen in Patients 70 Years of Age or Older), and 9344 (Doxorubicin Dose Escalation in Patients with Node-Positive Disease). Patients were asked to contribute peripheral blood (as a source of germline DNA and plasma) as well as urine. Permission was obtained to access tumor blocks for somatic DNA and immunohistochemical assays. Baseline epidemiologic information was obtained through a telephone interview, including detailed family history, reproductive history, smoking history, alcohol consumption, and diet. A follow-up psychosocial interview was administered to a subset of patients and included scales assessing overall quality of life (physical symptoms and functioning, psychological state, body image, and family/social/sexual functioning); breast cancer-specific anxiety; and screening behaviors and attitudes toward genetic testing. All of this information was linked to the CALGB clinical database, which contains treatment and follow up information. Because our primary goal was to evaluate the prognostic and predictive value of genetic testing in patients receiving defined treatments for breast cancer, we did not interview or collect germline DNA from family members and could not enroll volunteers outside CALGB-sponsored clinical trials.

To address issues concerning informed consent and patient confidentiality, the principal investigator of the grant supporting the project (O.R.M.) convened members of the Steering Committee of the project, National Cancer Institute staff, members of cancer patient advocacy groups, representatives from the Human Genome Project, and staff from the National Institutes of Health Office for Protection from Research Risks (OPRR) to assist in developing and reviewing the patient consent form for the registry. To maximize patient confidentiality, several layers of security were used to protect the database, and the ability to link the clinical data and genetic test results was restricted to a single senior biostatistician. When obtaining informed consent we agreed that patients should have the option of participating in some or all of the activities described in the protocol (provision of germline DNA, tumor tissue for somatic DNA and immunohistochemistry, plasma, urine, and the epidemiology questionnaires). Patients who elected to provide germline DNA for BRCA1 and BRCA2 testing could choose whether or not to receive test results. After further input from breast cancer advocates, a draft of the patient consent form was developed to include the following language:

"You have indicated below whether you wish to be contacted concerning results of genetic testing. You understand that certain of the tests used by CALGB for detection of heritable cancer genes are very new, have not yet been shown to be completely reliable, and may not have been approved by the FDA for diagnostic purposes. If you wish to be informed about the outcome of genetic tests carried out on your DNA, you understand that this information is preliminary in nature, should be investigated further with additional laboratory tests, and is provided to you with these reservations."

The consent form was submitted for approval by the Institutional Review Board (IRB) at each CALGB member or affiliate institution. Participation in data collection for the registry was limited to institutions in which genetic counseling was currently available or planned for the future. To increase the number of genetic counselors with expertise in the genetics of familial cancer, the CALGB initiated a program to educate appropriate members of the group with respect to such counseling. Three full-day workshops organized by leaders in the field of cancer genetics were held to assist institutions in acquiring the skills and resources necessary to be involved in the registry.

RESULTS

In the first year of accrual (October 1, 1995 to September 30, 1996), only 43 patients were enrolled in the registry. During the same period, 883 patients were enrolled in the clinical protocols from which patients could be drawn. Thus, only 5% of eligible patients were enrolled in the registry. Only 40 of 211 CALGB institutions (19%) approved the registry protocol, and, among these institutions, only 12 enrolled patients in the registry from 1995 to 1996.

The main reasons institutions did not approve the registry protocol were legal and ethical concerns regarding patient confidentiality. Although we advised institutions on possible techniques (e.g., encryption) for protecting sensitive databases, many remained skeptical of their ability to maintain confidentiality in dealing with the information we planned to provide patients. In an attempt to further protect confidentiality of genetic test results, CALGB obtained a Certificate of Confidentiality from the Department of Health and Human Services stating that under the Public Health Service Act (42 USCA 241[d], 1988), CALGB is "authorized to protect the privacy of the individuals who are the subjects of research by withholding their names and other identifying characteristics from all persons not connected with the conduct of that research." Although not tested in court, the Certificate aims to protect institutions from involuntary disclosure of research tests to insurance providers or employers.

We also encountered several problems with informed consent. Some institutions argued strongly that we should not administer a lengthy and complex consent form for genetic testing at the same time patients faced the multiple stresses of diagnosis and randomization to

treatment for breast cancer. During pilot testing of our psychosocial questionnaire, a number of patients reported they were not aware they had given permission for genetic testing. Questioning revealed that they understood they had agreed simply to provide tissue, blood, and urine for research.

When testing for BRCA1 and BRCA2 became commercially available, the Steering Committee elected to change the status of disclosure so that information from genetic tests would no longer be provided to patients enrolled in the registry or their providers. The consent forms for the companion treatment trials were amended accordingly to include a section describing the registry, followed by a checklist where patients could indicate whether or not they consented to use of tissue, blood, or urine for research purposes. The revised consent form stated, "Neither you nor your doctor will receive the results of genetic tests." Using a single consent form for both the treatment trials and the registry simplified the process of enrollment and obtaining informed consent. Removing the need for genetic counseling allowed us to open the registry protocol to all CALGB institutions and affiliates, regardless of whether they provided such services. Finally, because results of genetic tests would not be returned to the institution for conveyance to the patient, concern about the handling of confidential information at the institutional level was no longer an issue.

After implementing the above changes, accrual to the registry increased. In the second year of accrual, 79 patients were enrolled. However, several barriers to accrual remained. Many IRBs that approved the original informed consent refused to accept a single informed consent document for treatment trials and the registry. Some institutions remained concerned that CALGB could be held liable for withholding genetic test results, even though the tests were conducted as part of a research study. Consequently, accrual to the registry remained far below our expectations.

DISCUSSION

With the discovery of familial cancer genes, there has been widespread speculation that a comprehensive understanding of the human genome will allow accurate prediction of future health or risk of disease. Whereas some have expressed concerns that this view is too optimistic (15), the current availability of testing for cancer susceptibility genes is a reality that the public and the cancer treatment community must deal with. It is imperative that we make the most of information provided by genetic tests, especially if it proves useful in guiding treatment.

To investigate whether germline BRCA1 and BRCA2 mutations affect survival and/or predict response to specific forms of treatment for breast cancer, we attempted to establish a registry of breast cancer patients on CALGB-sponsored clinical trials. A total of 112 patients were enrolled in the registry during the first 2 years of accrual, far below the number of patients needed to address our primary research questions. Because germline mutations in BRCA1 and BRCA2 mutations are rare, a registry of several thousand patients is required. For example, assuming that 5% of breast cancer patients under age 40 years are carriers of BRCA1 mutations (16), approximately 3000 such patients would be needed to detect a 10% difference in disease-free survival between carriers and non-carriers with 80% power.

A major obstacle to establishing the registry was the problem of insuring confidentiality of genetic test results within a cooperative (i.e., multi-institutional) group setting. Review of the project at our institutions occurred at a time when concern about the linkage of information about individuals from multiple government and private databases came under wide scrutiny. Originally, we arranged to provide genetic test results to patients. A number of investigators and one institution argued strongly that the field was too new and laboratory methods too uncertain to provide such feedback. This argument was countered by those who believed it unreasonable and unethical to discover that a patient carried a germline mutation and withhold this information if the patient desired to know the result. Our decision to provide test results proved problematic because the protocol could be activated only at institutions with the ability to develop and support appropriate genetic counseling procedures. Even after conducting several genetic testing workshops, we found that providing genetic counseling for cancer patients remained an insurmountable obstacle for most institutions. In addition, many institutions were not confident of their ability to maintain confidentiality of genetic test results when this information was provided to institutions for conveyance to patients.

When testing for BRCA1 and BRCA2 became commercially available, we decided not to provide genetic information to patients or their providers. We believed that patients who wished to know their BRCA1 or BRCA2 status could be referred elsewhere. However, our decision not to provide genetic test results created problems for patients and providers. Many institutions did not approve the revised registry protocol because of concern that CALGB could be held liable for withholding genetic test results from patients. The cost of commercial genetic testing may have prevented patients from pursuing testing elsewhere. Recent evidence suggests that a large percentage of the public is interested in hereditary cancer risk notification and testing (17).

We encountered several problems with informed consent. To participate in data collection for the registry, breast cancer patients were asked to consent to the use of germline DNA at the same time they faced the stress of diagnosis and randomization to treatment. We sought to enroll patients in the registry at the time of initiation of cancer treatment in order to obtain pre-treatment DNA specimens so as not to confound assay results by exposure to cytotoxic chemotherapy. The inability of a number of patients who signed consents for our genetic studies to recollect a few weeks later that they had done so is a sobering reality. If it could be established that germline DNA collected during or after chemotherapy and/or radiation represented a resource equivalent to that of DNA collected before treatment, informed consent could be obtained at a time less stressful to the patient.

Other aspects of informed consent must be addressed for genetic studies involving cancer patients. Recent policy statements agree that informed consent is required for all genetic research in which results can be linked to individuals (18–20). Based on our experience, if patients are to be truly informed of the nature of the research in which they are participating, some genetic counseling is needed during the informed consent process. Currently, only half of NCI-sponsored cancer centers offer genetic counseling for cancer patients (21). It has been argued that patients should be fully informed of the use of DNA specimens, regardless of whether test results are to be provided (22). However, disclosure of all potential genetic testing is impossible for loci which have yet to be discovered. More important, listing of laboratory tests to be performed on consent forms may require patients to answer affirmatively to employers or insurers who inquire whether they have undergone genetic testing, even though they will not learn the results of the tests (23). Attention has been given to establishing guidelines for processing and storage of biologic samples (24), but the "ownership" (or control for purposes of research) of patient blood and tumor tissue remains a contentious issue, especially in cooperative groups (25). Finally, genetic studies carry strong negative connotations for members of some racial and ethnic groups (26) and could threaten a recent trend of greater participation of minority groups in cancer treatment trials (27).

Until more is known about the clinical implications of BRCA1 or BRCA2 status, there is little likelihood that there will be any benefit to patients who participate in data collection for cooperative group registries such as ours. This issue has likely exacerbated the problems of patient confidentiality and informed consent. We are committed to developing an appropriate method for conveying genetic test results to patients and their providers should insights be gained from our research that could benefit participants in the future. Delivery of such information depends on devising accurate laboratory screening methods to avoid misclassification of gene status (28), discovering strategies for minimizing the adverse psychological effects of genetic testing (29–30), and developing uniform standards for the scope of disclosure and future use of genetic samples (31). New strategies for protecting patient confidentiality in research, such as the designation of "tissue trustees," must be explored (32). A recent report issued by the National Institutes of Health Task Force on Genetic Testing (33) demonstrates that considerable progress is being made on these issues. We believe that genetic testing may some day help identify patients most likely to respond to treatment, sparing patients for whom the treatment will not work. Based on recent evidence that BRCA1 and BRCA2 may play a role in DNA repair (34–35), it has become increasingly important to evaluate the relationship between gene carrier status and response to ionizing radiation treatment and specific forms of adjuvant chemotherapy (36–38). For this reason, despite many obstacles, we believe studies of this type must go forward.

RECOMMENDATIONS

Following is our series of recommendations for future studies that involve genetic testing in cooperative groups. These suggestions may be useful as projects such as Cancer Genetics Networks (39) are established. Such studies require close collaboration between physicians, molecular biologists, psychologists, public health professionals, and most important, patients and patient advocacy groups (40–41).

1. Consensus building and agreement on goals is necessary at the design stage of cooperative group registries. To address anxiety among clinicians, institutions, and patients surrounding genetic testing, methods for addressing patient and institutional confidentiality must be agreed upon before such projects are implemented.
2. Protection from discrimination is essential for patients who participate in genetic research. Legislation is needed to prohibit insurers and employers from inquiring whether a patient has undergone genetic testing in a research setting.
3. A Certificate of Confidentiality issued by the Public Health Service is an important safeguard for genetic research. A long lead time for obtaining the certificate should be anticipated when the project is conducted among multiple institutions (42).
4. An agreement should be reached among federal and institutional bodies responsible for the protection of human subjects regarding appropriate methods for linking patient DNA samples with patient identifiers.
5. A consensus statement must be developed by patient advocacy groups, independent investigators, legal counsel, and administrators regarding standardized language for informed consent in genetic studies. In particular, the nature of genetic research and methods for safeguarding genetic information must be explained carefully to patients.
6. The number of genetic counselors with special expertise in familial cancer genes must be increased. Genetic counselors should participate in the process of informed consent for genetic studies, regardless of whether results are to be provided to patients.
7. Standards for disclosure or nondisclosure of genetic information to patients and their families must be developed. There is widespread disagreement among experts concerning the ethics of providing results of genetic tests to participants in research studies. In contrast to laboratory tests that are licensed for diagnostic purposes, genetic screening methods are often preliminary in nature and will, at times, lead to erroneous conclusions. If such information is to be disclosed to participants, appropriate counseling must be provided.

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BIOGRAPHICAL SKETCH

Give the following information for the key personnel and consultants listed on page 2. Begin with the principal investigator/program director. Photocopy this page for each person.

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Carolyn Compton, M.D., Ph.D.	

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Bryn Mawr College, Bryn Mawr, Pennsylvania	B.A.	1969	Biology
Harvard Medical School, Boston, Massachusetts	M.D.	1977	Medicine
Harvard Grad. School of Arts and Sciences, Cambridge, MA	Ph.D.	1977	Anatomy
Brigham & Women's Hospital, Boston, MA	AP/CP	1984	Pathology Residency

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Key personnel include the principal investigator and any other individuals who participate in the scientific development or execution of the project. Key personnel typically will include all individuals with doctoral or other professional degrees, but in some projects will include individuals at the masters or baccalaureate level provided they contribute in a substantive way to the scientific development or execution of the project. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

Academic and Clinical Appointments

1978-1981	Pathology Internship and Residency Brigham and Women's Hospital, Boston, MA
1981	Chief Resident in Pathology Brigham and Women's Hospital, Boston MA
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